# OPTIMISATION OF OXYTOCIN USE DURING LABOUR

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**ABSTRACT**

Both endogenous and exogenous oxytocin play a key role in the various stages of labour. Misusing this high-alert drug could lead to several maternal and foetal adverse outcomes. A suspected local overuse of oxytocin led to particular interest in this topic. This study aimed to investigate the local use of oxytocin, audit its use against local protocols and compare to international guidelines. The effects of such use on the mother and foetus were assessed.

A cohort prospective observation study was performed. The study was carried out at the Obstetrics wards, Mater Dei Hospital, Malta. A three-month collation of data was statistically analysed using IBM SPSS Version 27 One-way ANOVA, Pearson Correlation and Chi- Squared Test.

305 births were analysed. Statistical significance was obtained for the following correlations; a lower 1-minute Apgar Score, a longer first and second stage of labour with oxytocin use, a lower Apgar Score with prolonged second stage of labour; higher incidence of ventouse deliveries with a prolonged second stage of labour; and a shorter duration of labour with higher parity.

Disparities pertaining to the rate of the infusion being doubled sooner than the recommended time interval in the local protocol or starting the infusion at a higher rate than that recommended were observed in 7.7 % of the oxytocin group. Another deviation related to the higher than recommended use of maximum oxytocin units as per local protocol, which was observed in 4.3% of the oxytocin group.

The local oxytocin protocol was generally coherent with international guidelines, key differences being lesser detail in specific domains such as the management of uterine tachysytsole and absence of rates and regimens for nulliparous and multiparous mothers. The study highlights the need for optimising the use of oxytocin in the management of labour in view of the general lack a general consensus on recommended dose, regimen and administration rates. Further studies are recommended in order to approach standardisation.

**Keywords :**

Oxytocin, labour, protocol

**To Margie**

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**GLOSSARY OF TERMS**

| | |
|---|---|
| Antepartum | before childbirth |
| Augmented labour | the stimulation of labour when the process is progressing at a slower pace than normal |
| Dystocia | difficult labour |
| Perinatal period | during pregnancy |
| Postpartum | after childbirth |

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| CS | Caesarean Section |
| CTG | Cardiotocography |
| EDA | Epidural Analgesia |
| El/LSCS | Elective Low Segment Caesarean Section |
| Em/LSCS | Emergency Low Segment Caesarean Section |
| FHR | Foetal Heart Rate |
| MDH | Mater Dei Hospital |
| NPICU | Neonatal and Paediatric Intensive Care Unit |
| OT | Oxytocin |
| OTR | Oxytocin Receptors |
| PG | Prostaglandin |
| PPH | Post-partum Haemorrhage |
| SPC | Summary of Product Characteristics |
| VBAC | Vaginal Birth After Caesarean Section |

# CHAPTER 1

# INTRODUCTION

This chapter gives a general overview of the topic together with the rationale of the study. In the second part of the chapter, relevant points to the study will be researched and discussed.

### 1.1 Background Literature Review

Contrary to common perception, labour is not exclusively the result of the action of uterine stimulants but it is rather the physiological change brought about as pregnancy approaches term (Kota et al., 2013; Funai and Norwitz, 2020). This process is influenced by foetal and maternal input together with changes in the birth canal, denoted as passenger, power and passage respectively (Hutchison et al., 2020).

The 'multi process' nature of parturition renders the possibility of complications very high, putting the life of both mother and foetus at risk. Dystocia, which happens when no cervical dilatation occurs for more than two hours (Shmueli et al., 2018), might occur due to abnormal positioning of the foetus, inefficient uterine contractions and inadequate pelvic anatomy including abnormalities of the maternal pelvic soft tissues. Pharmaceutical interventions may have to be implemented in such cases to augment or induce labour. One of the most common interventions employed during labour is the use of Oxytocin (OT). Synthetic OT via slow IV infusion (e.g. Syntocinon®; Pitocin®) is used for induction or augmentation of labour (Royal Pharmaceutical Society, 2018). Khajehei (2017) reports that 30%-50% of women are augmented with synthetic OT, while induction is carried out in 50%-70% of women. Dystocia is the most common reason behind labour augmentation with OT and Caesarean sections (CS) (Duff, 2005). OT use during labour can be beneficial, however great caution must be put into practice due to the high-alert nature of this drug. OT may not only give rise to adverse outcomes during labour or shortly after birth, but also negative outcomes later in life, which

happen as a result of a disruption in the orchestration of natural hormones (Khajehei, 2017).

### 1.2 Oxytocin

OT, derived from the Greek words 'okus' and 'tokus' , which mean rapid and childbirth respectively, is an endogenous mammalian cyclic nonapeptide. OT was discovered by Sir Henry Dale in 1906 when extracts of human posterior pituitary gland induced uterine contractions in a pregnant cat (Simpson, 2011; Kim et al., 2017).

Pharmaceutical OT can either be extracted from mammalian sources or synthetically produced (Royal Pharmaceutical Society of Great Britain, 2018), with the latter process first materialising in 1953 by Vincent du Vigneaud (Simpson, 2011).

#### 1.2.1 Endogenous versus Exogenous Oxytocin

Endogenously, OT is synthesised in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and stored and secreted by the posterior pituitary gland into the bloodstream when hypothalamic cells are excited in both males and females (Kim et al., 2017), following several stimuli including sexual (like copulation) and non-sexual stimuli (like contact with offspring). The blood-brain barrier (BBB) hinders the endogenously released maternal OT from re-entering the brain.

During labour, this peptide is also produced in the amnion[1], the placenta and the decidua [2] (Khajehei, 2017).

While endogenous OT is released from the posterior pituitary gland in a pulsatile fashion, exogenous OT is administered via a continuous IV infusion during labour

[1] Amnion: the membrane surrounding the human embryo ( Oxford, 2021)

[2] Decidua: the thick layer lining the uterus during pregnancy (Oxford, 2021)

(Simpson, 2011). Both forms of OT exert effects on the body through OT receptors (OTR), but do not act in the same manner. Synthetic OT can give rise to unpredictable effects, which effects can vary according to administration site, route and dosing regimen. This potential for unpredictable effects can be explained by physiological differences in OTR during administration with synthetic OT. Such unpredictable effects are thought to influence the mother–child attachment, lactation and possibly the development of the child (Khajehei, 2017). For example as stated in this latter study, Khajehei (2017), the crossing of maternal, endogenous OT across the placenta and foetal BBB might offer a protective effect to the brain of the unborn foetus. This happens through the inhibitory action of the neurotransmitter gamma-aminobutyric acid, ultimately making the foetal brain less vulnerable to hypoxic damage during delivery through a series of nervous system changes in the foetal brain. In contrast, theoretically, due to the nature of the molecule, synthetic OT is unable to cross the BBB and therefore such nervous system changes cannot occur. The administration of high-dose OT regimens or atosiban, the OT antagonist, will result in the OTR block and a consequent reduction in the neuro-protective effect of OT, thereby making the foetus more vulnerable to hypoxic brain damage (Khajehei, 2017). Differences between the two forms of OT are summarised in Table 1.1 below.

**Table 1.1:** Summary of the activities of endogenous Oxytocin and Syntocinon®

| Endogenous OT | Syntocinon® |
|---|---|
| - Modulating neuroendocrine reflexes<br>- Preparation of foetal neurons for birth<br>- Uterine contractions<br>- Birth of the baby<br>- Facilitating milk ejection and breastfeeding<br>- Maternal behaviours (Behavioural adaptations to the maternal role; positive feelings and memory for facial identity)<br>- Bonding and attachment<br>- Stabilising social behaviours<br>- Partner and offspring preference | - Uterine contractions<br>- Birth of the baby<br>- Potentially increasing the foetus's vulnerability to hypoxic brain damage<br>- Myometrial ischaemia<br>- Increased sensation of pain<br>- Likelihood of abnormal foetal heart rate patterns, foetal distress and uterine rupture<br>- Impaired lactation and breastfeeding<br>- Maternal postpartum anxiety and depression symptoms<br>- Minimal affectionate touch and low levels of attachment behaviours and social synchrony |

Adopted from: Khajehei, M. Labour and beyond: The roles of synthetic and endogenous oxytocin in transition to motherhood. British Journal of Midwifery. 25. 230-238. 10.12968/bjom.2017.25.4.230.

### 1.2.2 Oxytocin Receptor System and Mechanism of Action

The oxytocin/oxytocin receptor system in labour is responsible for uterine contraction stimulation, in order to achieve expulsion of foetus and placenta (Kim et al., 2017; Page et al., 2017). The OTR increase in quantity function as term approaches and even more so during labour itself (Drummond, 2018). During spontaneous labour, adequate

OTRs are present, warranting lower doses of exogenous OT for labour augmentation. Higher doses would be required for labour induction, in which case a sub-optimal amount of OTRs are present (Khajehei, 2017).

Activation of OTR brings about the movement of calcium ions from the sarcoplasmic reticulum into the cytoplasm, activating protein kinase type C, leading to the contraction of smooth muscle via activation of Calcium-dependent calmodulin. In turn myosin light chain kinase activity is triggered (Kim et al., 2017).

During pregnancy and especially towards labour, OT levels rise, bringing about stronger uterine contractions to achieve vaginal delivery of the foetus. OT is one of the few hormones that works by a positive feedback loop mechanism i.e. the contractions brought about as OT is released, stimulate further OT production – the change brought about stimulates further instability in the body, unlike with other hormones which work by negative-feedback loops, with the scope of annulling the original stimulus (Osilla and Sharma, 2020).

During labour, OT stimulates cervical ripening by stimulating prostaglandin release upon activation of phospholipase A2 and cyclooxygenase II activity, the two major enzymes in prostaglandin synthetic pathway aiding in cervical effacement (Kim et al., 2017).

**1.2.3 Functions of Oxytocin**

Although the most known and most significant function of OT is presented on the myometrium during pregnancy and during parturition, OT exhibits a plethora of functions in both males and females, including maternal, social and sexual behaviour, lactation, erectile dysfunction and ejaculation (Simpson, 2011; Kim et al., 2017; Khajehei, 2017). Osteoporosis, diabetes, cancer and stress also seem to be affected by

OT (Simpson, 2011). OT is also used as an adjunctive therapy in some types of miscarriage or missed abortion (Royal Pharmaceutical Society of Great Britain, 2018).

### 1.2.4 Syntocinon®

Syntocinon® 10 IU/mL Concentrate for solution for infusion is the preparation of OT available and used at Mater Dei Hospital (MDH). It is a clear, colourless sterile solution provided in 1 mL clear glass ampoules. As per its Summary of Product Characteristics (SPC), OT is indicated as follows:

Antepartum:

- for the Induction of labour for medical reasons including post-term pregnancies, premature rupture of the membranes and pregnancy-induced hypertension (pre-eclampsia).
- for labour stimulation in hypotonic uterine inertia (the occurrence of infrequent, weak and short uterine contractions)
- as adjunctive therapy in early pregnancy for the management of incomplete, inevitable, or missed abortion.[3]

Postpartum:

OT is also used postpartum following Low Segment Caesarean Section (LSCS) deliveries and for the prevention and treatment of postpartum uterine atony and haemorrhage by helping the uterus to contract.

Exogenous OT is mixed with normal saline in the majority of cases. In mothers in whom sodium chloride intake should be avoided, dextrose 5 % can be used instead. OT administration is adjusted on a case by case basis i.e. the rate reduced or increased as

[3] Electronic Medicines Compendium (eMC). Oxytocin 10 IU/ml Solution for infusion - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd.; 2019 [cited 15 August 2020]. Available from: https://www.medicines.org.uk/emc/product/9334/smpc

deemed necessary. Following OT initiation a target outcome of 3-4 contraction every 10 minutes is sought. After achieving acceptable uterine activity, the infusion rate is reduced. The recommendation is that 5 IU of Syntocinon® are mixed with 500 mL of electrolyte solution and this infusion set at 1-4 mU per minute.

As soon as the OT infusion is started, continuous monitoring of foetal heart rate (FHR) and uterine activity is necessary. This enables the timely identification of uterine hyperactivity and/ or foetal distress, recognized as decreased variability or decelerations (FHR below the baseline heart rate) as a result of decreased blood flow to the placenta. This is carried out by means of cardiotocography (CTG).[4]

OT can only be given post 6 hours from the administration of vaginal prostaglandins. OT is never administered as a bolus injection due to the possible occurrence of an acute short-lasting hypotension with manifestation of flushing and reflex tachycardia, a phenomenon precipitated by a decreased venous return in turn causing a reduction in systemic vascular resistance or cardiac output (Archer et al., 2009).

#### 1.2.4.1 Pharmacodynamics and Pharmacokinetics

OT circulates in the bloodstream as a free 9-amino-acid peptide and is cleared from the plasma through maternal renal and hepatic routes. At term, its clearance rate is 19-21 mL per kg/minute. OT has a biologic half-life of 10 -12 minutes and steady state is reached after about 4 half-lives. Uterine response to OT is observed within 3 - 5 minutes following IV administration. Comprehension of such information is important to explore OT optimal dosing regimens (Simspon, 2011).

[4] Electronic Medicines Compendium (eMC). Oxytocin 10 IU/ml Solution for infusion - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd.; 2019 [cited 15 August 2020]. Available from: https://www.medicines.org.uk/emc/product/9334/smpc

### 1.2.5 Oxytocin Receptor Desensitisation

Being a G-protein coupled receptor, prolonged stimulation of the OTR leads to receptor desensitisation (Daniel-Spiegel et al., 2004), which happens in both spontaneous and non-spontaneous labour (i.e. induced and augmented labour) (Khajehei, 2017). The concentration and duration of the OT infusion will therefore affect the OTR system in the mother's body through receptor desensitisation, possibly prolonging labour. Khajehei (2017) reports that OTR desensitisation was significantly more pronounced in women who used Syntocinon® for longer periods of time. It was also reported that induction or augmentation of labour decreases OT mRNA concentration when compared to spontaneous labour (Khajehehi, 2017).

## 1.3 Oxytocin as a high-alert drug

OT is considered to be the most common cause of avoidable adverse perinatal outcomes. Due to its high propensity for harm, whose risk could be mitigated by adequate precautions, OT was classified as a high-alert drug in 2007 and added to the respective list of high-alert drugs of the Institute for Safe Medication Practices. This list includes drugs that can cause significant adverse events if they are inappropriately used. For this reason such drugs require special precautions and monitoring measures before and during their administration to protect the patient's well-being-; in this case at both the maternal and foetal ends (Krening et al., 2012).

Care is to be taken not to exceed the amount of OT necessary for normal labour progression and to appropriately evaluate the associated risks, maternal and foetal (Simpson, 2011). If not used as intended, OT use can lead to uterine hyper-stimulation resulting in various undesirable results such as uterine rupture, foetal asphyxia, or foetal hypertension (World Health Organisation, 2014). Changes in the FHR make up most of

the consequences of OT misuse following inappropriate detection and management of uterine tachysystole, which is defined as the occurrence of more than 4 contractions in 10 minutes over a period of 30 minutes (Mahlmeister, 2008; Krening et al., 2012). In a study by Mahlmeister (2008), it was observed that the foetal oxygen saturation was reduced by 20% in the event of 5 contractions in 10 minutes over 30 minutes. Similarly, a 29% reduction in foetal oxygen saturation was documented in the occurrence of at least 6 contractions in half an hour. Uterine tachysystole has been shown to be a significant obstetric liability (Krening et al., 2012).

OT protocols from various countries exist which vary from country to country or across different national institutions. Several dissimilarities pertaining to dose and regimen exist in these OT protocols without any specific regimen being particularly favoured. Therefore, clinical practice must be based on evidence-based guidelines (Rooks, 2009; Simpson and Knox, 2009) to avoid dose-related errors, which is the most common error when it comes to OT use. For example in the USA, as stated in a study by Mealing et al. (2009) there is a large discrepancy between the initial infusion rates for OT induction of 200 % - 300 %.

Due to its high alert status, such uterotonic drug can put the life of both mother and foetus at risk if not enough care and caution is effectively put into practice. Therefore, measures should be implemented to move towards a standardized use of OT rather than using it routinely, which could lead to its overuse and overdosing (Mahlmesiter, 2008; Rooks, 2009; Krening et al., 2012; Hidalgo-Lopezosa et al., 2016).

In view of these concerns, health care professionals in the delivery room must be made more aware of the risks associated with OT misuse and work by allowing more time for the mother to progress naturally rather than administering more OT, once uterine

activity is satisfactory. Studies show that OT infusion can be reduced or discontinued as soon as 5 cm cervical dilatation is reached (Mahlmesiter, 2008; Saccone et al., 2017; Boie et al., 2018).

### 1.4 Discontinuing OT during active labour

OTR desensitisation warrants research to evaluate the discontinuation of OT infusion once active labour is established (Daniel-Spiegel et al., 2004). Chopra et al. (2015) cited research by Ustunyurt and colleagues who had reported a longer, but statistically insignificant duration of labour when OT was stopped when active labour was reached. Spiegel et al. observed a shorter active stage of labour and lower incidence of caesarean deliveries in a group who had OT stopped at 5 cm cervical dilatation. This finding was also reported by Saccone et al. (2017). In view of the evidence that stopping OT infusion at active labour does not significantly prolong labour and does not exert any adverse outcomes on mother and foetus, such practice can be considered for settings where resources are limited. This is because less monitoring would be required, which would in turn also be more cost effective (Chopra et al., 2015). Contrastingly Girard et al. demonstrated significant increase of 113 minutes in the duration of labour in the group of mothers wherein OT was discontinued.

### 1.5 Labour classification

As defined by the WHO, a spontaneous onset, vertex foetal position together with satisfactory maternal and foetal conditions following spontaneous delivery describe normal labour (Selman and Johnston, 2013). Even though parturition is a natural course, due to suboptimal factors such as ineffective uterine contractions or abnormal foetal presentation, dystocia might occur, possibly warranting the need for interventions. For example, such interventions may be necessary if more than four

hours elapse with no cervical changes accompanied by satisfactory contractions or in the event of six hours with insufficient contractions. Both scenarios are considered to be labour arrest (Hutchison et al., 2020).

In a number of cases, parturition may have to be stared artificially, referred to as labour induction. There could be cases where spontaneous labour (natural labour) has started but for some reason the process is progressing at a slower pace than it should, so interventions are implemented to achieve the desired pace to reduce undesirable effects of prolonged labour on both the mother and the foetus. This is termed 'augmented labour'.

### 1.5.1 Induction of Labour

Induction of labour is the process of artificially stimulating labour at or before term (WHO 2011; Leduc, 2013). The ultimate goal of inducing labour is to deliver the baby through vaginal delivery, after analysing the situation and adopting the appropriate interventions, which could be mechanical or pharmaceutical. Labour is usually induced by using prostaglandins and OT or by manually rupturing the membranes. The indications for inducing labour are scenarios where the risk of continuing with the pregnancy are greater than the risks associated with labour induction namely bleeding, uterine hyperstimulation, uterine rupture, foetal distress and Caesarean Section (CS). The WHO recommends that in institutions where labour is induced, it is ensured that the facility is sufficiently equipped to cater for Emergency Caesarean Section (Em/LSCS) (WHO, 2011). Such instances where induction of labour is indicated include more than 41 weeks of gestation; early membrane rupture; maternal medical conditions like preeclampsia and diabetes mellitus; intrauterine growth restriction;

oligohydramnios[5]; multiple pregnancy; and vaginal bleeding (WHO, 2011; Leduc et al., 2013). Mozurkewich et al. (2009) reported a high grade recommendation for inducing labour at or beyond 41 weeks of pregnancy. This is due to the reduction in perinatal deaths and meconium aspiration syndrome.

OT is the most widely used labour induction agent and it is administered in half of all the births in the United States to induce or augment labour. Labour induction rates have been on the rise across the globe over the last decades and hence the associated concern of OT overuse has been an ongoing debate. Timing deliveries according to the parents` requests or the hospital's schedules might be contributing factors to an increase in such rates (Nooh et al., 2005; WHO, 2011). Such inductions are referred to as 'elective or social inductions' (Nooh et al., 2005).

Induction rates have increased from 9.5 % to 23.8 % over a 25-year period from 1990 to 2015 in the USA (Kenkel et al., 2019). Another study by Mahlmeister in 2008 states that the rate of induction of labour has increased from 9.5% in 1990 to 22.3% in 2005. As reported by Krening et al. (2012) there was a 125 % increase in the incidence of labour inductions between 1989 and 2001. Another study by Mealing et al. (2009) found that the consumption of OT for the induction of labour has been amplified, with or without the use of prostaglandins. On the contrary, it has been shown that there has been a decline in the use of prostaglandins alone. Because of this, several pharmaceutical interventions have been on the rise to facilitate childbirth. WHO recommends that the mother-to be should be monitored when she is being administered prostaglandins or OT to assess the reactions of the uterus and the foetus to OT (WHO, 2011). A study by Caruana et.al (2016) shows that there is a high rate of

[5] Oligohydramnios- deficiency of amniotic fluid

labour induction at MDH, wherein nearly half of these mothers undergo induction before term.

Induced labour is longer than spontaneous labour, with the most striking difference being in the latent phase of the first stage until 6 cm dilation is reached (Harper et al., 2012). This prolonged labour increases the risk of the need of CS, which is increased further in unfavourable cervix conditions. Thus, labour induction is only to be carried out when the chances of a successful vaginal delivery are estimated to be high, primarily by determining the cervical status. BMI (> 40 kg/$m^2$), maternal age over 35 years and estimated foetal weight more than 4 kg increase the risk of resorting to CS (Leduc et al., 2013).

**1.6 Bishop Score**

One of the most common adopted method for cervical status assessment is the Bishop Score, (Figure 1.1) a scoring system based on 5 criteria specifically cervical dilation, position, effacement, consistency of the cervix, and foetal station to determine the favourability of the cervix and therefore the likelihood of a successful vaginal delivery. Cervical dilation, effacement, and station can have 0 to 3 points, while cervical position and consistency are scored 0 to 2 points. The minimum value possible is 0 whereas the highest value possible is 13. Generally, a Bishop Score of 8 or more is considered to be favourable. A Score of 6 or less is considered to be unfavourable (Leduc et al., 2013; Wormer and Williford, 2020).The greater the Bishop Score, the more favourable the cervix. Other methods include trans-vaginal ultrasound, which measures the cervical length, internal os, diameter and the posterior angle (Ezebialu et al., 2015).

## Bishop scoring system:

| Score | Dilation | Position of cervix | Effacement | Station | Cervical Consistency |
|---|---|---|---|---|---|
| | (cm) | | (%) | (-3 to +3) | |
| 0 | Closed | Posterior | 0 – 30 | -3 | Firm |
| 1 | 1 - 2 | Mid position | 40 – 50 | -2 | Medium |
| 2 | 3 – 4 | Anterior | 60 – 70 | -1, 0 | Soft |
| 3 | 5 - 6 | -- | 80 | +1, +2 | -- |

**Figure 1.1:** Bishop Scoring System

Adapted from: Wormer KC, Williford AE. Bishop Scoring system [book].2020 [cited Aug 18 2021]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470368/

If unfavourable cervix conditions are identified, cervical ripening methods are initiated, which can be non-pharmaceutical such as membrane sweeping, membrane stripping and amniotomy or mechanical, the most common being the Foley catheter insertion method. Prostaglandin administration is the most commonly used method to ripen the cervix (Mozurkewich et al., 2011).

### 1.7 Prostaglandins for cervical ripening

Prostaglandins are arachidonic acid derivatives, which exist in various types. Prostaglandins involved in the process of cervical ripening and labour include PGE2 and PGF2α, which act on different receptor families namely the PGEP and PGFP receptors respectively. Prostaglandin receptors are present in the myometrium, cervix, trophoblast, decidua, and foetal membranes (Bakker et al., 2017).

PGE2, dinoprostone, is available as a tablet, pessary, or gel. Vaginal preparations are easier to administer than intracervical preparations, because they result in more timely vaginal deliveries (Leduc et al., 2013).

Dinoprostone has been observed to bring about cervical ripening through regulation of the synthesis of hydrophilic glycosaminoglycans, an increase in elastin activity and an increase in collagenase activity. It is a synthetic preparation chemically identical to PGE2. CS increases the mother's predisposition to uterine rupture. Therefore, PGE2 is not to be used after such an intervention (Leduc et al., 2013).

Misoprostol is a synthetic PGE1 analogue that is indicated for the prevention and treatment of gastric ulceration as a result of non-steroidal anti-inflammatory drugs use. When used as per its off-label use as a cervical ripening agent, routes of administration of misoprostol include the oral, rectal, sublingual and vaginal. Together with its low cost and its rapid onset of action, misoprostol is a potential alternative to PGE2. Both PGE1 and PGE2 demonstrate a reduction in CS rates (Leduc et al., 2013).

### 1.8 Oxytocin during labour

The baby's descent during labour and the resulting vaginal and cervical stretch receptor stimulation trigger endogenous OT release and stimulate uterine contractions. Endogenous OT reaches its highest levels at birth as the foetal ejection reflex is stimulated (Khajehei, 2017).

OT can be used to augment or induce labour and to control postpartum bleeding and uterine hypotonicity in the third stage of labour (Mahlmeister, 2008; Simpson, 2011; Page, 2017; Kajehei, 2017; Royal Pharmaceutical Society of Great Britain, 2018; Drummond, 2018). During the third stage of labour, immediately following birth, synthetic OT is administered intramuscularly to help the uterus contract and prevent post-partum-haemorrhage (Khajehei, 2017).

### 1.8.1 Oxytocin for postpartum haemorrhage prevention

Post-partum haemorrhage (PPH) is described by the WHO as at least 500 mL blood loss in the first 24 hours following delivery. One out of every four maternal deaths associated with child-birth is due to PPH, which in turn is caused by the unsuccessful active management of the third stage of labour (the delivery of the placenta). Therefore, the active management, rather than the expectant management of this final stage of labour is of utmost importance to reduce maternal morbidity and mortality. Expected management refers to the unaided progress of spontaneous placental delivery which could be facilitated by gravity. Active management on the other hand includes the use of a uterotonic drug namely OT to ensure efficient uterine contractions to avoid prolonged third stage and consequent PPH (Maughan et al., 2006).

The WHO guide, 'Managing complications in pregnancy and childbirth', states that a retained placenta is diagnosed if the third stage of labour lasts longer than 30 minutes following delivery of the baby (WHO, 2009).

For the prophylaxis of post-partum haemorrhage, OT may be used alone or in combination with other preparations namely ergometrine- Syntometrine®- 5 units OT with ergometrine maleate 500 mcg. As suggested in the British National Formulary, 10 units intramuscularly of OT may be administered alone, causing less nausea, vomiting and hypertension than the combination. Alternatively, 5 units of OT IV over 5 minutes or the Syntometrine® intramuscularly after delivery of the placenta can be given (Royal Pharmaceutical Society of Great Britain, 2018) or 20 units diluted in 500 mL normal saline (Maughan et al., 2006).

### 1.8.2 Oxytocin for labour induction and augmentation

When OT is administered exogenously during labour, it will have an added effect to the baseline maternal OT plasma concentration, aiding in the production of effective uterine contractions (Simpson, 2011). The use of OT for elective induction is off-label (Page et al., 2017).

According to ACOG, 39 weeks gestation must be completed for labour to be induced or foetal lung maturity is to be established before induction. In situations like gestational or chronic hypertension, preeclampsia, eclampsia, diabetes, premature rupture of the membranes, severe foetal growth restriction and post-term pregnancy induction of labour may be started according to ACOG. Contraindications of labour induction include transverse foetal position, umbilical cord prolapse, active genital herpes infection, and women who have had a previous myomectomy.[6]

Induction is carried out by OT when the cervix is already in a favourable condition i.e. the mother has a Bishop score of 6 or more. If the cervix is unfavourable, cervical ripening is first achieved by means of a prostaglandin to initiate the uterine contraction (Acharya et al., 2017).

Usually a solution containing 5 units in 500 mL of a physiological electrolyte solution like sodium chloride 0.9 % is used, but more concentrated solutions may be given via infusion pump. In the UK the initial rate of the OT infusion is 1 to 4 mU/min, which may be increased gradually by 1 to 2 mU/min, at intervals of at least 20 minutes until a maximum of 3 or 4 contractions are occurring every 10 minutes. In the USA, licensed dosage recommendations are lower than in the UK. Infusion rates are started at 0.5 to

[6] Kamal K. Labour Induction Guidelines by ACOG. Speciality in Medical Dialogues [Internet]. Speciality Medical Dialogues. 2017 [cited 21 May 2020]. Available from: https://speciality.medicaldialogues.in/labor-induction-guidelines-by-acog/

1 mU/min, and the dose is gradually increased in increments of 1 to 2 mU/min at intervals of 30 to 60 minutes.

Plasma oxytocin concentrations similar to those in spontaneous labour are observed at a rate of up to 6 mU/min. About 10 mU/min is usually the most that is needed at term, but doses of up to 20 mU/min or more may be required in situations such as labour induction at an earlier stage of pregnancy or for intra-uterine foetal death. If established labour is not reached after administering a total of 5 units, failed induction of labour is diagnosed. However, it may be repeated on the following day, starting again with a rate of 1 to 4 mU/min.

### 1.9 High-Dose versus Low-Dose Oxytocin Infusions

The influence of the OT dose (and a possible longer labour duration) on OTR desensitisation serves as a driving force to explore superior infusion doses. There seems to be no consensus about one particular OT dosing regimen that proves better outcomes. Studies have shown a positive correlation between the higher-dose regimens and a slightly shorter duration of labour, without an increase in CS incidence or adverse foetal outcomes. Such higher-dose regimens have also shown to be positively correlated with more occurrences of uterine tachysystole (Drummond, 2018).

A process-improvement project across a 9-hospital system in Colorado affected a standardized use of OT with low-dose infusions together with the routine completion of safety checklists (pre initiation and during administration of OT) for foetal and maternal well-being reassurance. This new protocol made use of the preparation of 30 units of OT in 500 mL IV fluid (1 mL/hr), a starting rate of 0.5 to 2 mU/min, which can be gradually increased by 1 to 2 mU/min every 30 to 60 minutes up to a maximum

dose of 20 mU/min. Following the implementation of this new standardised use, there was a statistically significant lower incidence of primary CS, shorter labour durations and a statistically significant reduction in the hours of receiving OT, and a statistically significant lower incidence of tachysystole (Krening et al., 2012). Another study by Tesemma et al. (2020) showed a significant association between high dose OT regimen and a minor reduction in the duration of labour and a higher occurrence of instrumental deliveries. Another study reported that the risk of having to perform a CS decreases by 15 % to 46 % when using the high dose OT regimens (4-10mU/min) rather than the low-dose regimen (1-4mU/min) without any adverse outcomes on mother and foetus. However, the high-dose regimen was found to be linked to a shorter duration of labour and higher incidence of tachysystole. Instrumental deliveries were carried out in both groups; in the high-dose for foetal distress and in the low-dose for failure to progress. Research has not yet found advantages of the routine use of high-dose OT regimens during labour.

**1.10 Adverse effects**

OT ADR's include uterine hyperstimulation with hypertonic or tetanic contractions, leading to uterine rupture and soft tissue damage. Effects in the foetus include bradycardia, arrhythmias, asphyxiation, and potentially death. If OT administration is prolonged, water retention might occur possibly leading to hyponatraemia and intoxication, which may lead to convulsions, coma or even death. Other adverse effects include headache, nausea and vomiting, rashes, cardiac arrhythmias, pelvic haematoma, and anaphylactic and other hypersensitivity reactions (Royal Pharmaceutical Society of Great Britain, 2018).

Due to its similar structure to antidiuretic hormone, OT has shown that it also exerts antidiuretic effects possibly leading to water intoxication via water overload. Although this is unlikely to happen when OT is indicated for labour induction or augmentation, when administered in relatively high doses for a prolonged period of time, such as in postpartum haemorrhage and abortion extra care has to be taken in keeping infusion doses low and restricting fluid intake (Sasaki,2008).

### 1.11 The 'multi process' nature of labour

Several physiological changes occur during the final month of pregnancy, bringing about the onset of labour (Selman and Johnston, 2013; Kota et al., 2013). These changes are complemented by several other changes, as shown in Figure 1.2 below, namely a decrease in progesterone and a consequent increase in oestrogen. The rise in oestrogen levels leads to the up-regulation of the OTR in the myometrium, hypothalamus and pituitary gland thereby causing increased sensitivity to OT. The increased prostaglandin synthesis in the uterus, increased myometrial gap junction formation, decreased nitric oxide activity and increased influx of calcium into myocytes, increased endothelin allow increased uterine blood flow and myometrial activity and the activation of the foetal placental hypothalamic-pituitary-adrenal axis (Kota et al., 2013; Khajehei, 2017).

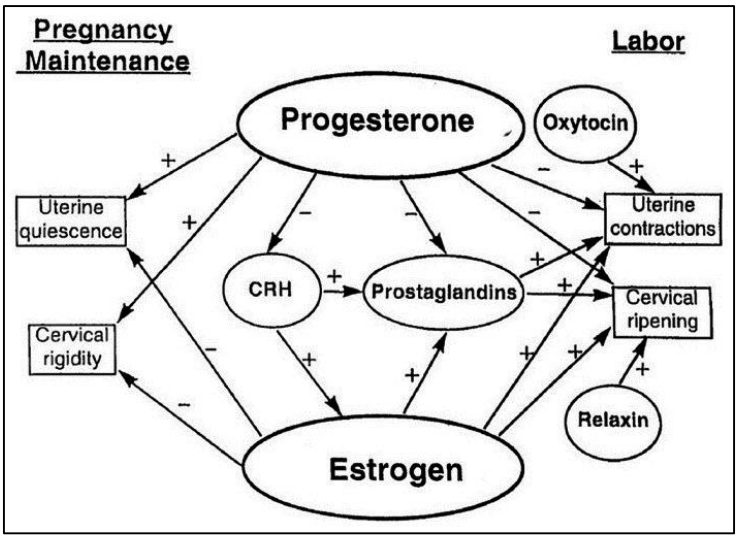


**Figure 1.2:** Endocrinological control of pregnancy and parturition in women. The balance between the effects of oestrogen and progesterone is critical to maintenance of pregnancy and the onset of labour. Other important hormonal factors modulate this balance as shown.

Adopted from: Kota SK, Gayatri K, Jammula S, Kota SK, Krishna SV, Meher LK, Modi KD. Endocrinological control of pregnancy and parturition in women. The balance between the effects of oestrogen and progesterone is critical to maintenance of pregnancy and the onset of labour. Other important hormonal factors modulate this balance as shown in the scheme [Image].2013 [cited Aug 18 2021]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659907/

Albeit it being a continuous process, labour is divided into three main stages of different duration the first stage, which is further subdivided in the active, latent and transitional phases; the second stage, which is the time from full dilatation to the birth of the baby; and the third stage (the delivery of the placenta) (Hutchison et al., 2020). In 1954, Emanuel Friedman determined the 'normal' duration of the first two stages of labour and the Friedman's S-shaped graph was developed (Cesario, 2004). According to Dr. Friedman, the first stage of labour should not last longer than 28.5 hours and 2.5 hours is the maximum duration for the second stage of labour (Duff, 2005).

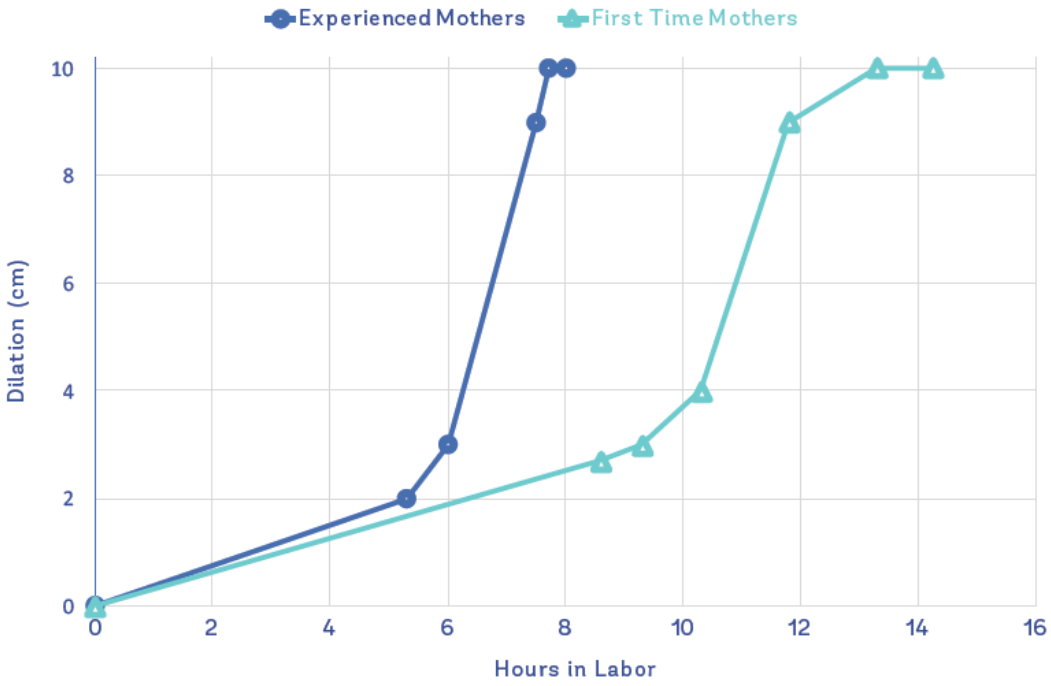


**Figure 1.3:** Friedman's Curves (1955-1956)

Adapted from: Duff M. A study of labour [Image]. 2005 [cited Aug 18 2021]. Available from: https://opus.lib.uts.edu.au/bitstream/10453/20169/2/02whole.pdf

The first stage is further subdivided into 3 phases; namely the latent phase, the active phase and the transitional phase. During this first stage, the cervix dilates fully to 10cm. The onset of labour can be determined when the mother experiences strong, regular contractions 3-5 minutes apart (Hutchison et al., 2020). [7, 8]

The first stage of labour can be said to be delayed if there is cervical dilation of less than 2 cm in 4 hours for nulliparous women, if there is cervical dilation of less than 2 cm in 4 hours or a slowing in the progress of labour for multiparous mothers or if there is a change in the strength, duration and frequency of uterine contractions. The second

[7] National Health Service (NHS). What happens during labour and birth-Your pregnancy and baby guide your pregnancy and baby guide [Internet].United Kingdom: NHS; 2020: [cited May 9 2020]. Available from: https://www.nhs.uk/conditions/pregnancy-and-baby/what-happens-during-labour-and-birth/

[8] The National Institute for Health and Care Excellence (NICE). Intrapartum care for healthy women and babies

stage covers the period from which the cervix is fully dilated up to the birth of the baby, which is estimated to last about 3 hours for nulliparous women and 2 hours for multiparous women. The third stage is the delivery of the placenta (Selman and Johnston, 2013).

In local practice, breech presentations are mostly delivered by El/LSCS. However, recent studies have shown that for appropriately chosen candidates, a vaginal breech delivery is an option, as neonatal mortality and morbidity do not differ greatly than if delivery was to be achieved by El/LSCS. Additionally, a number of benefits have been proven. This leads to the need of review of current local guidelines on breech presentations deliveries (Fenech and Grech, 2020).

**1.12 Caesarean Section**

A Caesarean Section (CS) delivery is a surgical procedure by which a foetus is delivered through an incision in the mother's abdomen and uterus. This intervention can either be planned, referred to as elective CS- known well before the due date, for example if the baby is larger than normal or in breech presentation or in the case of multiple birth cases or if the mother has had previous caesarean deliveries. However, it can also be unplanned and performed unexpectedly, termed emergency CS. This happens mostly when labour induction fails[9]. It is thought that the implementation of simpler interventions could help reduce the incidence of CSs (WHO, 2011; WHO, 2014).

Around the time of the discovery of Friedman curve of the stages of labour (Figure 1.3), if successful vaginal delivery was not achieved within the time determined by this curve this was resolved by performing a CS. This could be justified by the unavailability

[9] American College of Obstetricians and Gynecologists (ACOG). Cesarean Birth Frequently asked Questions Labour, Delivery and postpartum care FAQ006. [Internet]. 2015 [cited 21 May 2020] Available from: https://www.acog.org/-/media/For-Patients/faq006.pdf

of technological methods to reassure maternal and foetal well-being during labour (Cesario, 2004). However, even after the development of several monitoring measures that can be employed during parturition, the rate of CS have been increasing all over the world (Betrán et al., 2007; Costley and East, 2012) with an increase from 4.5% in 1970 to 24.4% in 2001 in the USA (Cesario, 2004).

The procedure of a CS starts with an abdominal incision, which could be horizontal or vertical. This is followed by an incision in the uterine wall through which the baby and placenta are delivered. The incision is finally stitched back in place. For CS, the mother can be given general anaesthesia, an epidural block or a spinal block. If the mother is given general anaesthesia, she will not be awake during surgery. Associated complications with CS include blood loss and infection. [9]

### 1.13 Vaginal Birth after Caesarean[10]

Vaginal Birth after Caesarean (VBAC) raises some concerns in view of the risk of rupture of the scar left after CS because of the high pressure in the uterus during childbirth. This risk is greater in the incidence of a weaker not-side-to-side incision from the previous CS, when the mother has had surgical gynaecologic procedures in the past and when the scar has caused problems in previous labours.

While some interventions or injuries will not occur during CS such as an episiotomy and the consequent risk of infection or injury to the vaginal area, several affects are associated with CS. These include compromised physical health for at least the first

[9] American College of Obstetricians and Gynecologists (ACOG). Cesarean Birth Frequently asked Questions Labour, Delivery and postpartum care FAQ006. [Internet]. 2015 [cited 21 May 2020] Available from: https://www.acog.org/-/media/For-Patients/faq006.pdf

[10] Childbirth Connection. Research and Evidence [Internet]. Washington. National Partnership for Women & Families; 2020 [cited May 19 2020]. Available from: http://www.childbirthconnection.org/giving-birth/vbac/research-evidence/

two months after birth, not establishing breastfeeding (which is beneficial to both mother and baby). With VBAC, no incisions are made, so there is less risk of infection and pain in the vaginal area.

Research says that overall, VBAC is safer than CS for a number of reasons, not only for the pregnancy in question but also for any future pregnancies. Although the risk of the scar rupturing is there, evidence shows that this is low. Foetal mortality from VBAC is less likely than with CS. A common risk for both VBAC and a repeat CS is the possibility of having to perform an emergency hysterectomy.

Besides the fact that a mother who has undergone CS has to spend a longer time at hospital and a higher probability to be re-admitted. CS being a major surgical procedure poses a number of physical problems for the mothers, including haemorrhage, blood clots, bowel obstruction, severe pain and infection.

Prostaglandins, which act as cervical ripening agents, weaken the scar as they soften the cervix. OT increases the intensity of uterine contractions and the pressure within the uterus during labour. For these reasons, such agents increase the risk of scar rupture during VBAC.

**1.14 Analgesia**

Endogenous OT also has an analgesic role during labour. This is achieved mainly through the blockage of the β-adrenergic receptors and the consequent increased level of endorphins in the blood, particularly β-endorphins, which will in turn bind more to the opioid receptors, giving rise to pain relief (Khajehei, 2017).

Childbirth brings with it a great deal of pain that can interfere with the mother's performance during delivery through catecholamine release and hypocapnia. The consequent constriction of uterine blood vessels and the reduced ventilator drive of

the mother between contractions contribute to the reduction in foetal oxygen supply, increasing the risk of foetal hypoxemia, hypoxia and foetal metabolic acidosis (Lam et al., 2020).

The term analgesia refers to pain relief without losing consciousness (Schrock and Harraway-Smith, 2012) and the notion of pain relief during labour dates back to 1853 when chloroform was administered to Queen Victoria as she was giving birth to her eighth child (Pang and O'Sullivan, 2008).

Mothers-to-be should be educated about the available pain relief methods during the antenatal period explaining strengths and limitations of each and together with the medical team select the most appropriate one for them. Pain relief methods include both pharmacological and non-pharmacological methods such as hydrotherapy, (which is contraindicated when OT is used for labour induction (Cowan et al., 2017) due to the decrease in OT levels following hydrotherapy initiation) (Kilgore, 2007); inhalational analgesia; systemic opioid analgesia; and regional analgesia (Pang and O'Sullivan, 2008), which is further subdivided into epidural and spinal analgesia, or a combination of both referred to as walking epidural (Schrock and Harraway-Smith, 2012). Constant support during labour from the partner and the healthcare team is very beneficial and increases the likelihood of spontaneous vaginal birth, leads to less requirement for analgesia, and more positive experiences (Pang and O'Sullivan, 2008).

### 1.14.1 Epidural analgesia

Although anaesthetic agents are used in epidural analgesia (EDA), rather than producing a total lack of feeling, which is the aim of general anaesthesia, lower spinal segment blockade is produced, rendering the mother less sensitive to sensation in the lower half of the body. This allows the mother to actively participate during labour. In

a regular epidural, an indwelling catheter is placed into the epidural space and a continuous infusion or multiple injections of local anaesthetic are administered to the parturient. Walking epidural is the combination of epidural and spinal blocks. This combination allows the mothers to move around (Schrock and Harraway-Smith, 2012).

### 1.14.2 Epidural and the second stage of labour

A study by Cochrane for Clinicians states that when compared to other types of analgesia or no analgesia altogether, EDA was shown to be more effective. However, a longer second stage of labour, an increased possibility of instrumental vaginal delivery, the incidence of maternal fever, and the possibility of OT administration were shown to be positively correlated with EDA administration (Shmueli et al., 2018). This prolonged second stage can be exhilarated by the decreased sensation of the mother on epidural, owing to the motor blockade and weakening of the pelvic floor muscles which in turn reduce the spontaneous maternal urge to push actively during the second stage of labour (Cesario, 2004; Mousa et al., 2012; Shmueli et al., 2018), which is absent with dilute anaesthetics. Contrasting evidence shows that EDA can shorten labour duration as maternal catecholamines are reduced during effective pain relief methods like EDA, exposing the uterus to less inhibitory influence when it comes to contractility (Mousa et al., 2012).

### 1.14.3 Epidural and the need for augmentation with Oxytocin

The study by Mousa and colleagues (2012) lead to the conclusion that labour was not prolonged in the epidural group, but there was a statistical significance between this same group and the need for augmentation with OT to maintain the average duration of labour and also a significant higher infusion rate in the epidural group . This is also evidenced by Oscarsson et al. who stated that OT use increase four–to five fold when

EDA was administered. This is reflected in the co-occurrence of high OT use rates and high epidural use rate in hospitals (Oscarsson et al., 2006).

Friedman's labour graph, which was mentioned earlier needs to be reviewed in view of the various confounding factors which affect the duration of labour namely the shape of the foetal skull in relation to the maternal pelvis, increased foetal size along the years as a result of better nutrition (Cesario, 2004).

**1.14.4 Epidural and endogenous hormones**

PG-F2α, β-endorphin, and inflammatory cytokines are reduced when EDA is administered during parturition (Herrera-Gómez et al., 2018). The administration of EDA has been associated with a reduction in the production of endogenous OT production, warranting the higher associated use of OT in this population (Rahm et al., 2002; Herrera-Gómez et al., 2018). This element can possibly explain the prolonged second stage of labour following EDA. From an investigation by Rahm and colleagues, a negative association was found between OT use and EDA use. Conversely, higher plasma OT levels were found in women labouring spontaneously without EDA (Rahm et al., 2002).

**1.15 Anaesthesia**

General anaesthesia, local anaesthesia and EDA (which uses anaesthetic agent) are the forms of anaesthesia, which can be adopted. The active participation from the maternal end during labour is important. Therefore, general anaesthesia during labour is very rarely used. Instead, regional anaesthesia is used, whereby only sensation in the affected area is lost. Local anaesthesia is not used to reduce the pain of contractions but to provide sensation of numbness in the affected area. Often, local anaesthesia is

used after birth of the baby to relief the effects of any instrumental interventions such as episiotomy (Silva and Halpern, 2010).

### 1.16 Continuous Foetal Monitoring

All throughout OT infusion administration, the foetal well-being, expressed as FHR and uterine contractions respectively, is monitored continuously by means of CTG. This aims for the Health Care Professionals (HCPs) to intervene timely and appropriately, if necessary, preventing any harm to both mother and baby (Schneider, 2014) which included the reduction or discontinuation of OT administration (Preti and Chandraharan, 2018).

The normal value for FHR is 110–160 bpm and reflects the oxygen supply to the foetus, changes of which affects variability or gives rise to accelerations or decelerations and tachycardia or bradycardia. Such variability indicates the healthy function of the nervous system of the foetus (Schneider, 2014).

Multiple factors may influence the FHR, the misapprehension of which may lead to incorrect interpretation of the CTG and consequent inappropriate obstetric interventions. Gestational age and foetal behavioural states are the factors that exert the strongest effects on the FHR curve. For example, during foetal deep sleep phases, which are demonstrated by the foetus in late pregnancy there is a significant, almost no variability, which can be misjudged as hypoxia. In such cases, diagnosis can be aided by the use of stimuli to wake the foetus or by allowing the reading to go on for more than 40 minutes. CTG changes as a result of these factors occur in response to physiological changes, not because of some problem during childbirth; therefore, they can be classified as false positives, which make up around 50% of FHR patterns. This

leads to a greater incidence of inducted parturition and operative deliveries (Schneider, 2014).

The increase in the intensity and frequency of uterine contractions following OT administration could lead to suboptimal relaxation periods between contractions which could lead to decreased foetal blood supply. As stated by Mahlmeister in 2008 and by Ayres-de-Campos and Arulkumaran in 2015, the foetal oxygen saturation is very minimal, 90 seconds following the peak of a contraction in spontaneous labour and is normalised only after about another 90 seconds (Mahlmeister, 2008; Ayres-de-Campos and Arulkumaran, 2015), which period increases to 138 seconds in OT-induced labour (Ayres-de-Campos and Arulkumaran, 2015). When contractions are too frequent (more than 5 in 10 minutes over 20-30 minutes) or too long (more than two minutes) or, as can happen with OT overuse, the risk of foetal hypoxia is significantly increased. This in turn increases the risk for neonatal seizures, permanent neurological injury and foetal mortality (Mahlmeister, 2008).

Findings from studies show a greater incidence of CS and less neonatal seizures when CTG is perfumed continuously (Alfirevic et al., 2017). There have been debates on the pros and cons of continuous versus intermittent foetal monitoring (Edward Mullins et al., 2017).

**1.17 Apgar Score**

The Apgar score (AS) is defined by Appearance-skin colour, Pulse, Grimace-reflex irritability, Activity-muscle tone, and Respiration make up this score, which can range from 0 to 10 with each component carrying a maximum of two points. Like other assessment scores such as the BS, the AS is influenced by a number of factors including gestational age, birth weight, any medication administered during pregnancy and

labour itself and congenital abnormalities (Simon et al., 2020). Maria et al. in 2015 investigated how a prolonged second stage of labour affects foetal well-being by conducting a population-based cohort study in Sweden. Altman et al. reported that low ASs at 1 minute and NPICU admission are linked to longer second stage durations. Prolonged labour is commonly augmented with OT, the use of which can result in uterine hyperstimulation and consequent foetal distress. This leads to a low AS. (Altman et al., 2015).

### 1.17.1 Apgar Score and Oxytocin

A significant correlation was reported between OT use and an AS of less than 7 at 5 minutes and changes in the umbilical cord. A higher risk to develop metabolic acidosis (was also documented. Admission to neonatal intensive care units is significantly higher following OT use. This could be explained by the fact that OT use carries a high risk of uterine hyperstimulation, even more so when using high-dose OT regimens. The foetus will be in distress during uterine hyperstimulation as a result of very little, almost negligible oxygen concentrations travelling to the placenta during hyperstimulation which is then manifested as compromised foetal well-being. It was found that uterine hyperstimulation and the consequent foetal distress occur less when the OT dosing interval is increased, for example from 15 to 40 minutes. However, the adverse neonatal outcome could also be attributed to the actual indication of OT (Oscarsson et al., 2006).

Studies show that lower ASs have a positive correlation with induction of labour. In 2010, Matais et al. revealed that delayed lactation and unsuccessful breastfeeding can be the result of low ASs. Such correlation are however not consistent with findings of

other authors who documented no significant association between synthetic OT administration for labour induction and low AS (Khajehei, 2017).

### 1.18 Oxytocin and Lactation & Breastfeeding

Endogenous OT stimulates prolactin release from the pituitary gland. OT release is then further stimulated by nipple stimulation during breastfeeding, which bind to receptors in the mammary glands, aiding in the milk-ejection reflex. Breastfeeding is facilitated by endogenous OT, by boosting the mother's confidence and allowing her to be more relaxed. This has been demonstrated by Schwarze et al. in 2014 who reported that breastfeeding mothers were less stressed than non-breastfeeding mothers and the former also had higher plasma OT levels. Furthermore, during breastfeeding, endogenous OT stimulates uterine contractions that aid in reducing the size of the uterus postpartum and to decrease postpartum lochia (Khajehei, 2017). Synthetic OT appears to affect the initiation of breastfeeding in a dose-dependent manner through different ways. The antidiuretic effects of OT (owing to the molecular similarity with vasopressin), can give rise to breast engorgement and problems during breastfeeding. Delayed lactation and failed breastfeeding may be caused by the higher stress and anxiety levels from the maternal end, which in turn can be caused by the strong and painful nature of the contractions, brought about following synthetic OT administration. Exogenous OT also contributes to impaired neonatal suckling. Low ASs and other undesirable effects linked to labour induction and augmentation that hinder the new- born to have synchronised suckling, swallowing and breathing, may be the cause of such undesirable effects on lactation and breastfeeding (Khajehei, 2017).

### 1.19 Maternal outcomes

Besides these findings, Hidalgo-Lopezosa et al. (2016) also found a positive correlation between OT use and maternal fever during birth. Furthermore, a positive relationship has also been demonstrated between high body mass index, elevated maternal temperatures and the time between membrane rupture and delivery. EDA had no influence on such elevated temperatures. The reduction of endogenous OT after exposure to synthetic OT increase the maternal predisposition to developing postpartum anxiety and depression, decreased affectionate touch, low attachment and social behaviour. Animal studies have shown that maternal behavioural patterns determine OT organisation in the brain of the off-spring (Khajehei, 2017).

### 1.20 Oxytocin and Social Effects

The disruption in the natural hormone system at birth following synthetic OT administration might affect social behaviours, a phenomenon which is demonstrated by several animal studies. Studies show that Syntocinon® administration during parturition may alter the child's DNA methylation and consequently the neuropeptide systems in the child's brain. Findings from a study based in the US documented an association between induction or augmentation of labour and the likelihood of the child to develop autism spectrum disorders. Due to the possible contribution of other confounding factors such as any underlying obstetric or medical conditions, further research was suggested. Earlier studies found no association between synthetic OT use and autism diagnosis (Khajehei, 2017).

### 1.21 Aims and Objectives

In view of the above body of evidence, this study aimed to first investigate the local use of OT in Malta's acute general hospital, MDH, secondly compare local protocol and

international guidelines and finally evaluate the effects on the mother and foetus following OT administration.

# CHAPTER 2

# METHODOLOGY

This chapter describes the chosen study design, the inclusion and exclusion criteria adopted and the implemented search strategies. Ethical considerations that were required prior to carrying out the project will be recounted.

## 2.1 Setting

The study was undertaken at two Obstetric postnatal wards; Obstetrics 1 and Obstetrics 3, at the Department of Obstetrics and Gynaecology, Mater Dei Hospital (MDH) after obtaining the necessary approvals from Hospital Management and the University of Malta Research Ethics Committee.

## 2.2 Study Design

A copy of the local OT protocol followed was obtained. At the beginning of the study, the different units of the Obstetrics and Gynaecology Department at MDH were identified. The Department is made up of one antenatal ward: Obstetrics 2; two postnatal wards: Obstetrics 1 and Obstetrics 3, one labour ward and one gynaecology ward. It was also learnt that locally, breech presentations and multiple pregnancies are delivered by EI/LSCS.

## 2.3 Data Extraction

Data was then collected prospectively from patient files from Obstetric Wards 1 and 3 over a period of three months: July 2019 to September 2019. Considering that the minimum duration of the hospital stay following normal deliveries at the selected time was 48 hours, the respective clinical areas were visited on alternate days, where the pertinent patient files present on the day were accessed.

A cohort prospective observational approach was chosen. This approach was deemed the most suitable as it would provide a snapshot of the current practice, which is the

scope of the study. Furthermore, this prospective approach has a number of advantages over retrospective studies. These include the absolute control by the researcher in the data collection methodology and less selection bias (Hammoudeh et al., 2018). Cohort studies investigate the exposure and the outcome of a group of people.

Both qualitative and quantitative approaches were adopted in this investigation. The analysis and comparison of different international OT guidelines and the local OT protocol characterises the qualitative aspect of the study. The quantitative aspects enabled the identification of statistical significances between the factors to be considered (Table 2.1).

**Table 2.1:** Factors Compared

| **Factor** | **Contrasting Factor** |
|---|---|
| OT , nulliparous | No OT, nulliparous |
| OT, multiparous | No OT, multiparous |
| OT, Bishop score– favourable cervix | OT, Bishop score-unfavourable cervix |
| OT > 40 weeks | OT< 40 weeks |
| No OT > 40 weeks | No OT < 40 weeks |
| PG gel before OT | No PG gel before OT |
| OT for induction | OT for augmentation |
| OT, mode of delivery | No OT , mode of delivery |

## 2.4 Local Protocol and International guidelines

International guidelines were searched in scientific databases including PubMed; PubMed Central; Cochrane Database and Systematic Reviews; and Medline Complete (EBSCO). The search terms included were: 'Oxytocin guidelines' and 'Oxytocin guidelines for induction and augmentation of labour'. The majority of the results related to the third stage of labour or were not available as full text, rendering them irrelevant to the study. Consequently, articles which were deemed relevant were looked into and their reference list was vetted. A number of international guidelines were selected from the reference lists if they were appropriate. A Google and Google Scholar search was also performed. The search results were vetted accordingly and only guidelines concerning induction and augmentation of labour were selected. Guidelines relating to the prevention and treatment of postpartum haemorrhage were disregarded as this was beyond the scope of the study. Identified guidelines were then appraised, and compared and contrasted with each other and against the local protocol. Search results are detailed in Table 3.24 in Chapter 3.

## 2.5 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were set in order to select relevant patient files as follows:

**Inclusion Criteria**

- Cases evaluated from July 2019 to September 2019
- Singleton pregnancies
- Cephalic Presentation

**Exclusion criteria**

- Elective Low Segment Caesarean Sections (El/LSCS) which included multifoetal and breech pregnancies (since in Malta such cases are delivered via El/LSCS)

El/LSCS cases were excluded as such mothers would not have gone into labour in a natural way, which falls beyond the scope of this study.

### 2.6 Study Tools

Prior to data collection, a checklist (Appendix 1), was developed and was followed during data extraction. Parameters that were considered essential for the study included parity, gestational age, OT indication and Apgar scores at 1 and 5 minute. This checklist was validated by three experienced obstetricians from the Department of Obstetrics and Gynaecology, Mater Dei Hospital.

### 2.7 Data Analysis

Following data extraction, the necessary calculations were carried out to determine the following:

- the amount of OT units administered,
- duration of OT infusion,
- the duration of labour,
- The Bishop Score

Analogous calculations (Appendix 2) to the one above were worked out for all cases to determine the amount of OT units administered at the different rates (6 mL/hr, 12 mL/hr, 24 mL/hr, 48 mL/hr and 96 mL/hr) for different durations throughout labour, finally calculating the total amount of OT units administered and the total duration of infusion administration. For the purpose of this study only OT used up until the delivery of the baby was analysed i.e. only OT used in the first and second stage of

labour, excluding OT used in the third stage of labour (aiding in placental expulsion) and post-partum to help the uterus contract, as this is irrelevant to the aims of the study.

### 2.7.1 Calculations

Upon finding out how much OT was used in each individual case, the duration of labour was calculated for all mothers. In some cases, this was readily documented in the patient file as shown in table 2.2 below, taking the values as an example.

**Table 2.2:** Duration of Labour readily in patient files

| **Stage of Labour** | **Time taken ( hours and minutes)** |
|---|---|
| Duration of 1st stage | 6 hrs 30 mins |
| Duration of 2nd stage | 1 hr 10 mins |
| Duration of 3rd stage | 30 mins |
| **Total duration of labour** | 8 hrs 10 mins |

The 1st stage of labour (time taken to reach full dilation-10 cm) translates into the time from start of regular contractions to the end of 1st stage. The 2nd stage (from full dilation-10cm- to the birth of baby) translates into the period from end of 1st stage to time of delivery. In a few cases, neither were available, so they were omitted due to missing data.

In data inputting, duration of labour was expressed as duration of 1st stage, duration of 2nd stage and the total duration of labour, to analyse better the influence of OT on the different stages of labour.

In others cases this was calculated from other data available in the patient file as shown in Table 2.3 and 2.4 below.

**Table 2.3:** Calculating Duration of Labour alternatively

| **Progress of labour** | **Time** |
|---|---|
| Start of regular contractions | 13.00 |
| Time of rupture of membranes | 13.00 |
| End of 1st stage | 17.00 |
| Time of delivery | 17.31 |
| 3rd stage completion | 17.40 |

**Table 2.4:** Example to Table 2.3

| **Stage of Labour** | **Time** |
|---|---|
| Duration of 1st stage | 2 hours |
| Duration of 2nd stage | 31 minutes |
| Duration of 3rd stage | 9 minutes |
| **Total duration of labour** | 2 hours 40 minutes |

Mothers who ended up going for Em/LSCS, irrespective of the reason, were considered in a different statistical calculation, other than that for normal vaginal delivery cases. This is because such a procedure could have been carried out in view of various reasons like no progress and/or foetal distress, not necessarily following OT administration. Including such cases in the same calculation could lead to spurious results.

### 2.7.2 Calculating the Bishop Score

The next step was to calculate the BS, using the scoring system shown in Figure 1.1.

A BS of 8 or more is considered to be favourable. A Score of 6 or less is considered to be unfavourable (Leduc et al., 2013; Wormer and Williford, 2020).

After completing all data sorting, data was processed further in IBM SPSS version 27 for generation of statistical tests. Tests were carried out to compare the duration of labour and the foetal well-being in different scenarios. Table 5 below shows factors that were considered for data analysis, including parity, gestational age, OT indication, mode of delivery and the foetal well-being expressed as Apgar scores at 1 and 5 minutes.

### 2.8 Sample Characteristics

After data inputting, general characteristics of the sample were generated including mean maternal age and mean gestational age, percentage of Em/LSCS that were performed following OT use as well as the percentage of instrumental deliveries completed after OT administration and any NPICU admissions following OT use.

### 2.9 Statistical Analysis

A Null Hypothesis (NH) and an Alternate Hypothesis (AH) were set for each correlation, which were accepted or rejected according to the p-value obtained from the statistical test chosen. The 95% Confidence Interval (CI) was adopted for this study. A graphical representation was then generated for each relationship using SPSS version 27.

The NH specifies that the mean scores vary marginally between the groups and is accepted if the p-value exceeds the 0.05 level of significance (correlation coefficient is close to 0). The AH specifies that the mean scores vary significantly between the group and is accepted if the p-value is less than the 0.05 criterion (correlation coefficient significantly different from 0).

For any correlation between a categorical and a numerical factor, the One-Way ANOVA test was carried out. The one-way ANOVA test was used to compare mean scores between two or more independent groups namely and it was run for the following correlations: duration of labour with OT use, AS at 1 and 5 minutes with OT use, duration of second stage with mode of delivery, maternal age with OT use, amount of OT units with OT indication, duration of labour with prostin administration before OT and amount of OT units with prostin administration before OT.

For any correlation between two categorical factors, the Chi-Squared Test was carried out. The Chi-Square Test was in turn used to investigate the association between two categorical variables namely: OT administration with mode of delivery and OT use with prostaglandin gel administration.

For any correlation between any two numerical factors, the Pearson Correlation Test was carried out. The Pearson Correlation Coefficient measures the strength of the relationship between two continuous variables and it ranges from -1 to 1. This was carried out for the following correlations: Apgar score at 1 minute with duration of second stage of labour, duration of second stage of labour with OT units, maternal age with duration of labour, maternal age with amount of OT units used, amount of OT units used with time taken to reach maximum cervical dilation (first stage), OT use with parity, duration of labour with parity, OT units administered with gestational age, amount of OT units used with favourability of cervix- BS.

### 2.10 Em/LSCS Analysis

All Em/LSCS cases were then grouped and categorised according to the reason for performing Em/LSCS. Any correlations with OT were tested for.

### 2.11 NPICU cases

All NPICU admissions were analysed and correlations with OT were tested for.

### 2.12 Calculation to check for adherence to protocol

The cases in which OT was used (N=143) were carefully analysed to determine adherence to the current local protocol. This was performed as follows:

The maximum amount of OT units a mother could be administered if she were to be administered the full rate according to the local protocol (96 mL/hr) were worked out using the duration of infusion for each case. An example is shown below.

The amount of OT units for each rate that could be administered in 15 minutes (the local OT dosing interval) were calculated (Table 2.5). Provided that the Syntocinon® infusion used locally is 10 IU in 500 mL:

**Table 2.5:** Calculating Maximum OT units according to local protocol

| Infusion Rate (mL/hr) | Maximum OT units according to local protocol per 60 minutes (units) | Maximum OT units according to protocol per 15 minutes (units) |
|---|---|---|
| 6 | 0.12 | 0.03 |
| 12 | 0.24 | 0.06 |
| 24 | 0.48 | 0.12 |
| 48 | 0.96 | 0.24 |
| 96 | 1.92 | 0.48 |

After the first hour of infusion administration, the maximum amount of OT units a mother could be administered is (0.03+0.06+0.12+0.24) = **0.45 units**

Beyond the first hour, the remaining OT units were calculated using the maximum local rate according to protocol; **1.92 units**.

For example;

If the duration of OT infusion was 3.75 hours, the maximum amount of OT units that mother could have been administered is 1.78 units (0.45x1hr) + (1.92x2.75hrs).

Then, the difference between the used and calculated OT units and percentage difference were calculated for each case to determine if the actual OT units used were within range of the local protocol or not.

### 2.13 Ethical Considerations

Prior commencement of the study, permission to undertake this project was granted by the Hospital's Chief Executive Officer (Appendix 4.1) and the Data Protection Officer (Appendix 4.2). Moreover, approval was also granted by the Chairman of the Department in Obstetrics and Gynaecology and the other eight consultants providing care in the department to allow data collection from patient files under their care (Appendix 4.3). The research project was also approved by the Faculty Research Ethics Committee, University of Malta (Appendix 4.4).

# CHAPTER 3

# RESULTS

This chapter deals with the results of the study, expressed also as graphical representations. First some general data on the sample will be specified, after which statistical results to address the main and subsidiary research question will be presented. Such results will also be expressed graphically. The local protocol will be described and any deviations will be mentioned. International guidelines are tabulated with the local protocol and compared.

### 3.1 Sample size

Out of the 392 cases reviewed, 316 met the inclusion criteria. 143 mothers used OT; 113 did not use OT; 33 mothers ended up going for emergency C-section and 16 cases had to be omitted due to missing data, leaving a total of 305 cases for evaluation (Figure 3.1). 59 % of the mothers were Maltese and 41 % were of foreign origin.

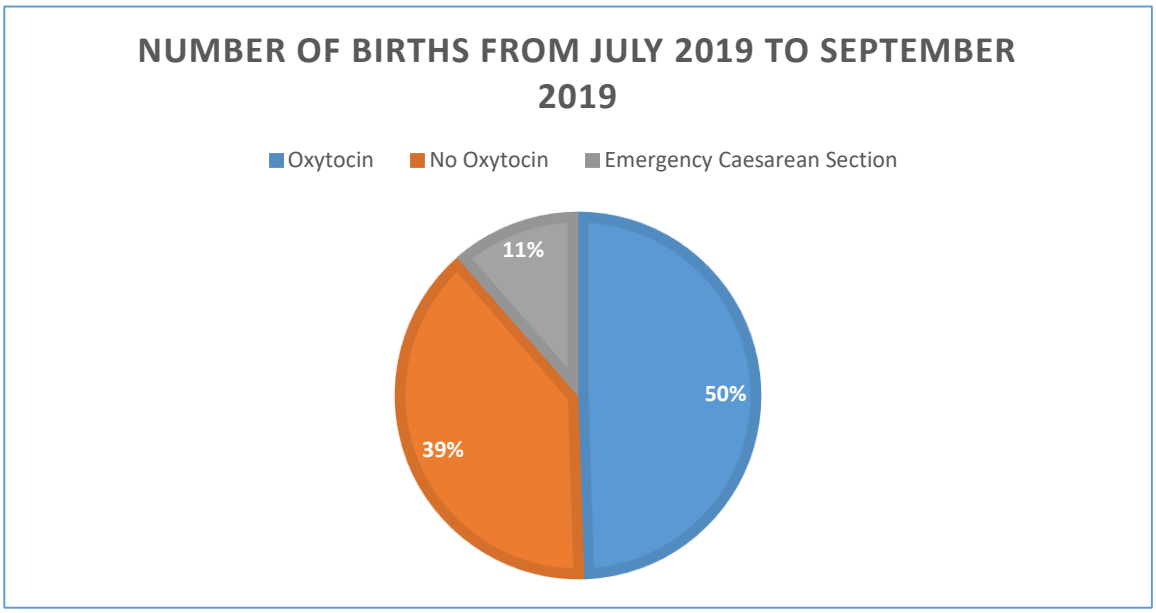


**Figure 3.1:** Total Number of Births (N=305)

### 3.2 Sample characteristics

The mean maternal age of the sample was 29.60 years with a mean gestational age of 39.35 weeks. 37.9% of the mothers were nulliparous, while 62.1% were multiparous. The mean amount of OT units used was 4.16 units and the OT infusion was administered for a mean duration of 4.56 hours. OT was used for induction in 51.75 % of the cases, while 48.25 % of the mothers were administered OT for labour augmentation. The mean duration of labour ($1^{st}$ and $2^{nd}$ stage of labour) was 5.79 hours. The mean BS was 4.68.

### 3.3 Statistical Analysis

For all correlations that follow, a NH and an AH were formulated, as explained in chapter 2. The 0.05 level of significance was adopted throughout.

### 3.3.1 Correlating Duration of Labour with amount of OT units used

**Table 3.1:** Duration of Labour and Amount of OT used

| One-Way ANOVA | | | | | | |
|---|---|---|---|---|---|---|
| OT use | Sample size | Mean Labour Duration | Std. Deviation | p-value | 95% C.I. for Mean Labour Duration | |
| | | | | | Lower Bound | Upper Bound |
| Yes | 143 | 5.97 | 3.442 | 0.275 | 5.39 | 6.54 |
| No | 113 | 5.53 | 2.808 | | 5.00 | 6.05 |

The NH is accepted-the mean scores for the duration of labour with and without OT use do not vary significantly statistically.

The error bar graph displays the 95% CI of the actual mean labour duration when OT is used and not used. The fact that these two CI's overlap indicate that the two mean labour durations do not differ significantly.

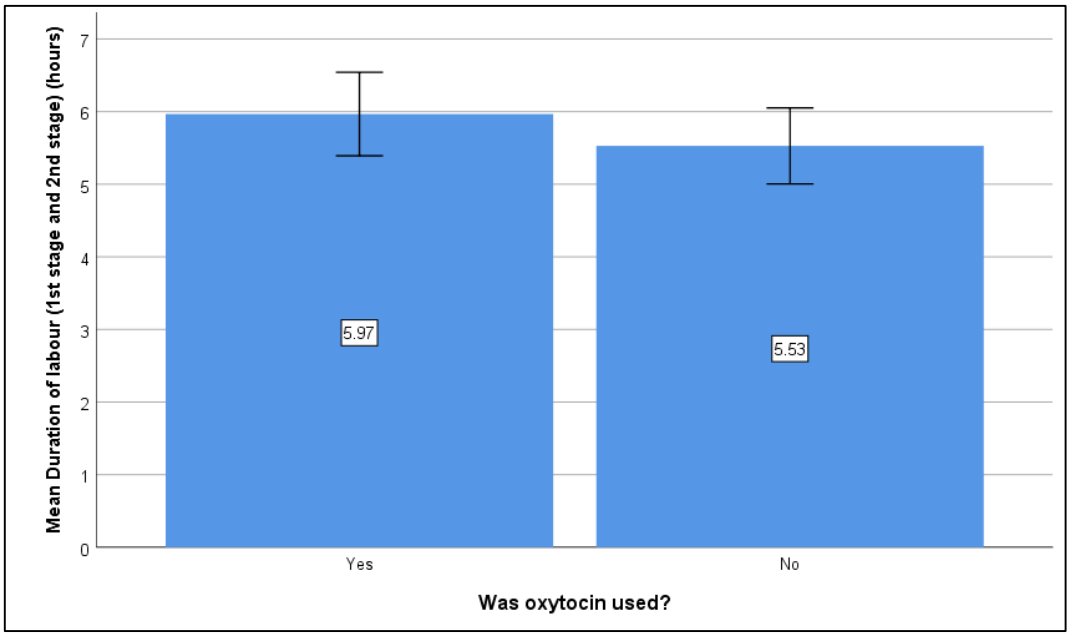


**Figure 3.2:** Mean duration of labour (1st and 2nd stage) against OT use

### 3.3.2 Correlating OT administration and mode of delivery

**Table 3.2:** Mode of delivery

| Chi-Squared | | | | | |
|---|---|---|---|---|---|
| | | | Was OT used? | | |
| | | | Yes | No | Total |
| Mode of delivery of this pregnancy | Normal | Count | 127 | 110 | 237 |
| | | Percentage | 88.8% | 97.3% | 92.6% |
| | Ventouse | Count | 16 | 3 | 19 |
| | | Percentage | 11.2% | 2.7% | 7.4% |
| Total | | Count | 143 | 113 | 256 |
| | | Percentage | 100.0% | 100.0% | 100.0% |

$X^2(1) = 6.690$, $p = 0.010$

The NH is accepted- there is no association between the 2 categorical variables. This is shown in Figure 3.3 below.

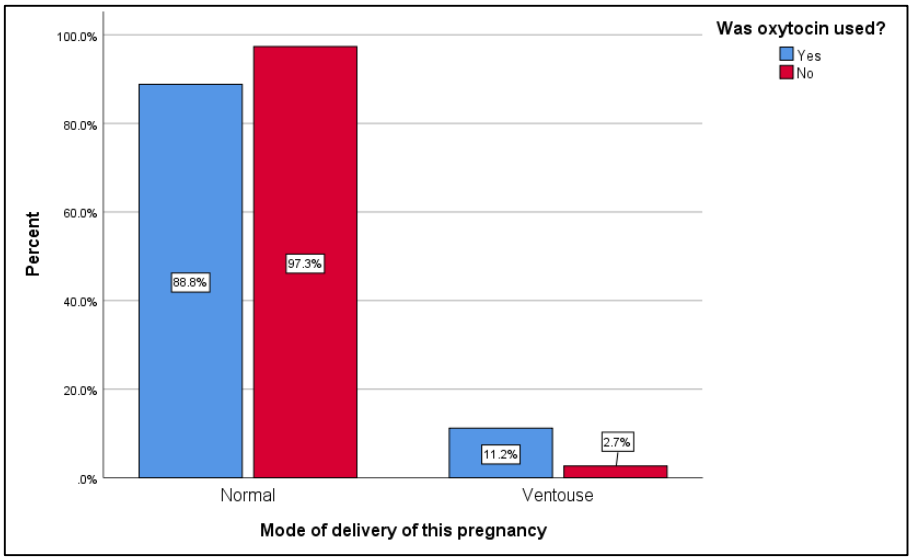


**Figure 3.3:** Percentage of Mode of Deliveries varies with OT use

### 3.3.3 Correlating Apgar Scores at 1 minute with OT use

**Table 3.3:** Apgar Score at 1 minute and OT use

| One- Way ANOVA | | | | | | |
|---|---|---|---|---|---|---|
| OT use | Sample size | Mean Apgar Scores at 1 minute | One-Way ANOVA Test | p-value | 95% Confidence Interval for Mean Apgar Score at 1minute | |
| | | | | | Lower Bound | Upper Bound |
| Yes | 143 | 8.59 | 1.170 | 0.048 | 8.40 | 8.79 |
| No | 113 | 8.83 | 0.549 | | 8.73 | 8.93 |

The AH is accepted-Apgar Score at 1 minute is significantly less when OT is used. This negative correlation is represented by Figure 3.4 below.

The error bar graph below shows the 95% CI of the actual mean Apgar scores at 1minute in the two populations. The two CI's overlap very slightly, indicating that the mean Apgar do differ significantly.

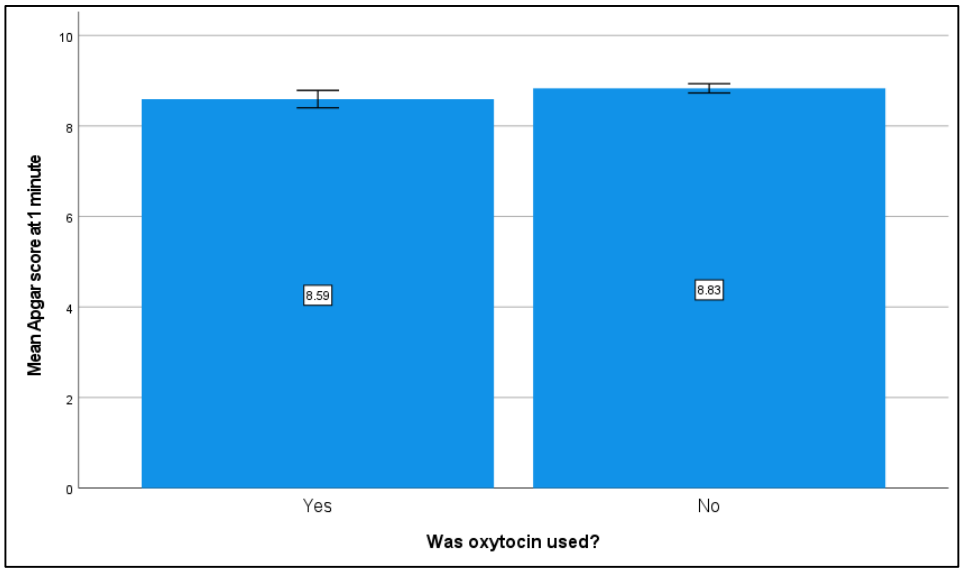


**Figure 3.4:** Mean Apgar Score at 1 minute against OT use

### 3.3.4 Correlating Apgar Score at 5 minutes with OT use

**Table 3.4:** Apgar Score at 5 minutes

| One- Way ANOVA | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% Confidence Interval for Mean Apgar Scores at 5 minutes | |
| OT | Sample size | Mean Apgar Scores at 5 minutes | Std. Deviation | p-value | Lower Bound | Upper Bound |
| Yes | 143 | 8.98 | 0.717 | 0.141 | 8.86 | 9.10 |
| No | 113 | 9.09 | 0.367 | | 9.02 | 9.16 |

The NH is accepted-the difference in the mean Apgar score values at 5 minutes is not statistically significant.

The error bar graph below (Figure 3.5) shows the 95% CI of the actual mean Apgar scores at 1 minute in the two populations. The two CI's do not overlap, indicating that the mean Apgar scores do not differ significantly.

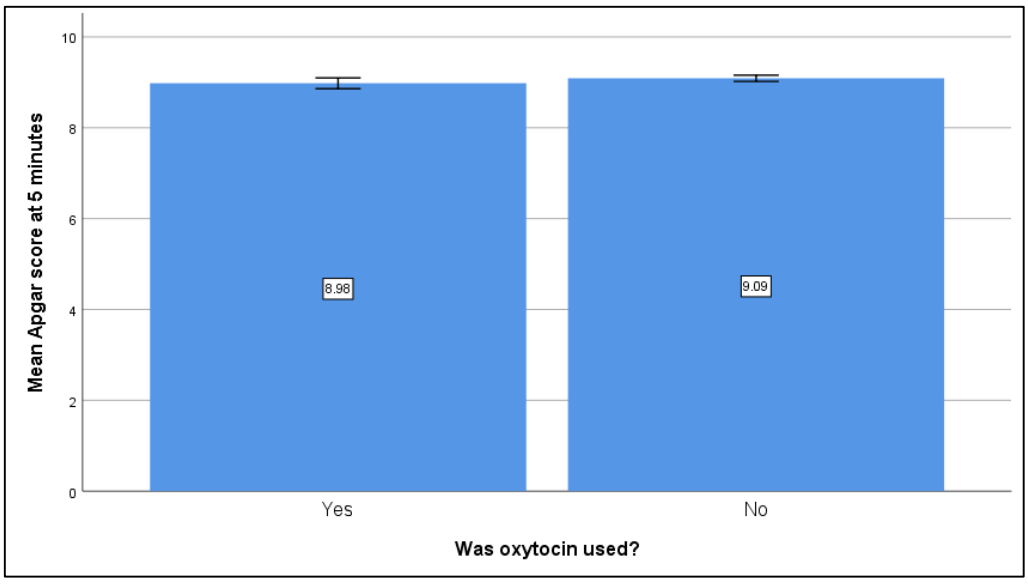


**Figure 3.5:** Mean Apgar Score at 5 minutes against OT use

### 3.3.5 Correlating Apgar Score at 1 minute with Duration of second stage of Labour

**Table 3.5:** Apgar Score at 1 minute with Duration of second stage

| Pearson Correlation | | |
|---|---|---|
| Apgar Score at 1 minute | Pearson Correlation | -0.330 |
| | p-value | 0.000 |
| | Sample size | 256 |

AH accepted- there is a significant relationship between the two variables.

This is displayed in Figure 3.6 below.

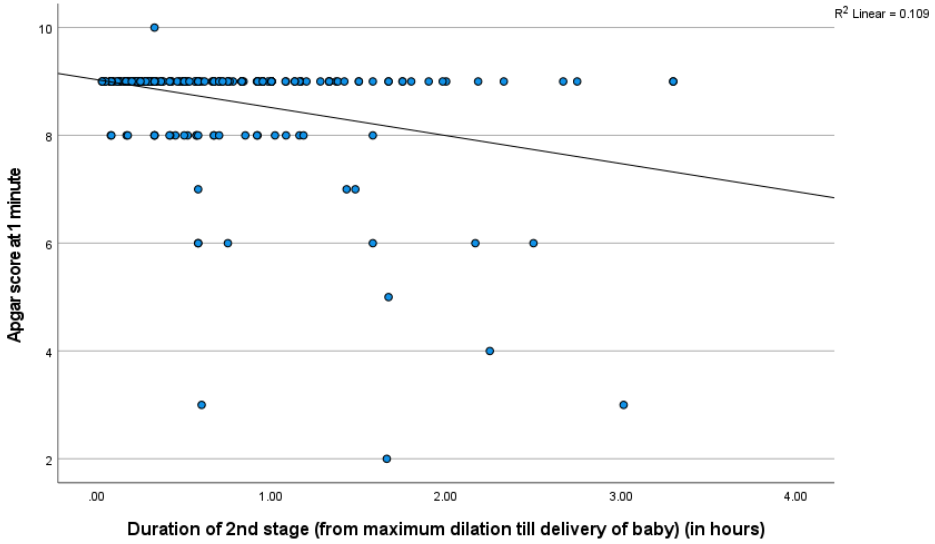


**Figure 3.6:** Apgar Score at 1 minute against the duration of the second stage of labour

### 3.3.6 Correlating second stage of labour with Mode of Delivery

**Table 3.6:** Second stage of Labour with Mode of Delivery

| One-Way ANOVA | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% Confidence Interval for Mean Duration of 2nd stage | |
| | Sample size | Mean of duration of 2nd stage of labour | Std. Deviation | p-value | Lower Bound | Upper Bound |
| Normal | 237 | 0.61 | 0.561 | 0.000 | 0.533 | 0.677 |
| Ventouse | 19 | 1.30 | 0.872 | | 0.844 | 1.741 |

The AH is accepted- the mean scores vary significantly. This significance is shown in Figure 3.7 below.

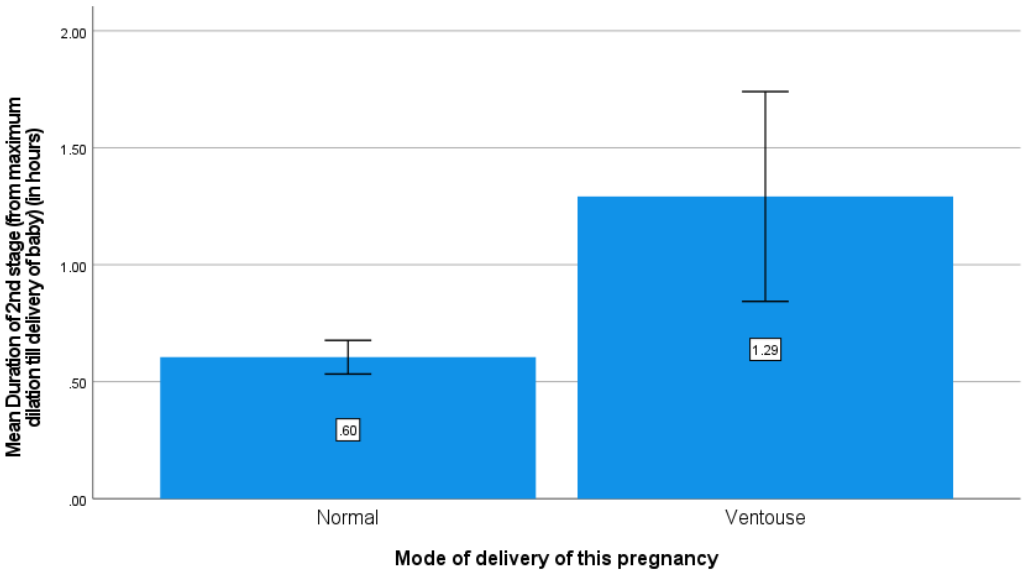


**Figure 3.7:** Mean duration of the 2nd stage of labour against the mode of delivery

### 3.3.7 Correlating Maternal Age with OT use

**Table 3.7:** Maternal Age and OT use

| One-Way ANOVA | | | | | | |
|---|---|---|---|---|---|---|
| | Sample size | Mean age of mothers | Std. Deviation | p-value | 95% Confidence Interval for Mean Maternal Age | |
| | | | | | Lower Bound | Upper Bound |
| Yes | 136 | 29.85 | 5.185 | 0.385 | 28.97 | 30.73 |
| No | 107 | 29.27 | 5.152 | | 28.28 | 30.26 |

NH accepted – Mean ages of the two populations vary only slightly. This is also displayed below by the error bar graph (Figure 3.8) in the overlap of the two CIs.

This error bar graph displays the 95% CI of the mean maternal age and the use of OT. The fact that these two CIs overlap indicate that the two mean labour durations do not differ significantly.

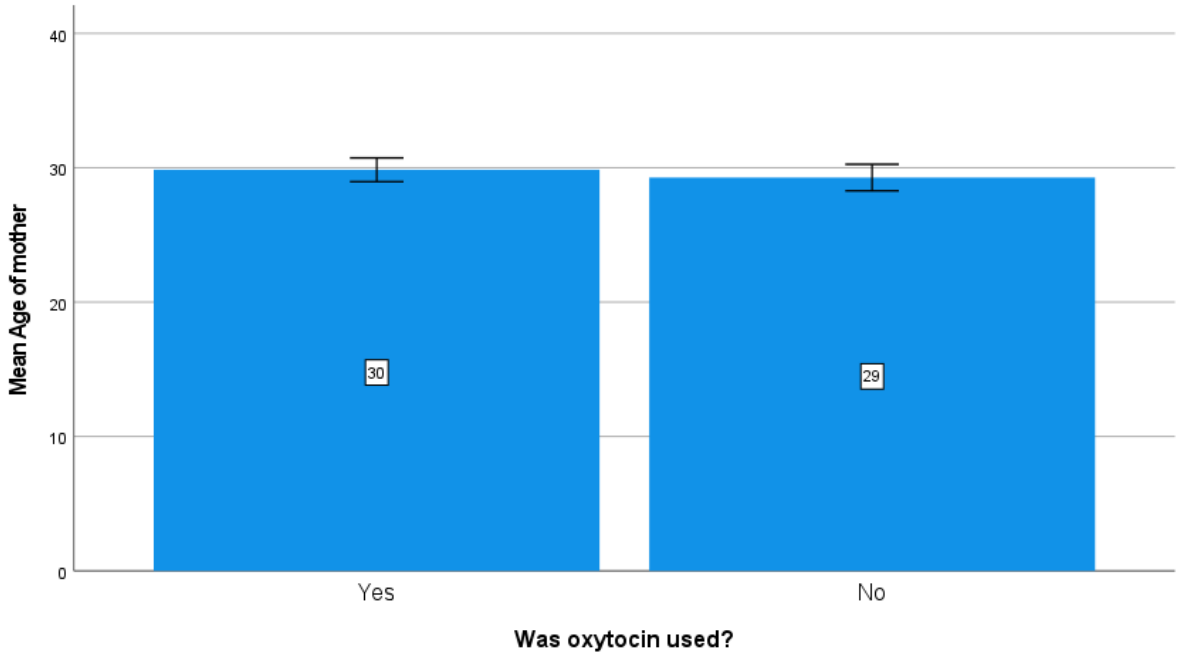


**Figure 3.8:** Mean maternal age against OT use

### 3.3.8 Correlating Age with Duration of Labour

**Table 3.8:** Maternal Age with Duration of Labour

| Pearson Correlation | | |
|---|---|---|
| Age of mother | Pearson Correlation | -0.107 |
| | P-value | 0.097 |
| | Sample size | 256 |

NH is accepted - there is no relationship between the two variables. This weak negative relationship is shown in Figure 3.9 below.

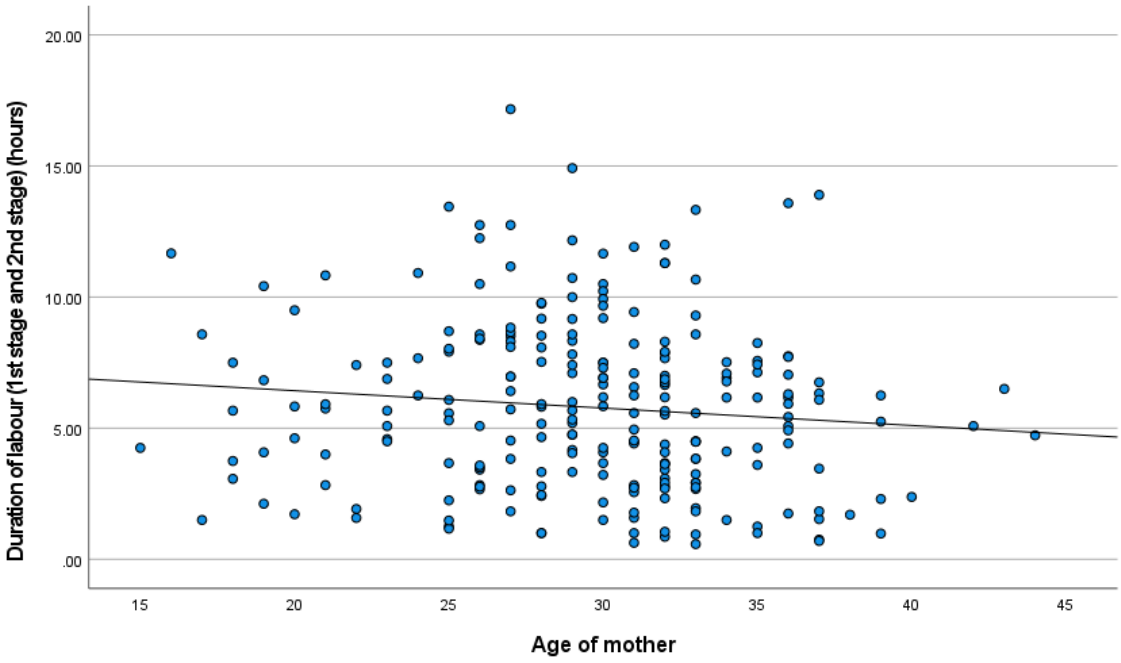


**Figure 3.9:** Duration of labour (1st and 2nd stage) against maternal age

### 3.3.9 Correlating the Age of the mother with the Amount of OT units used

**Table 3.9:** Age of mother with Amount of OT

| Pearson Correlation | | |
|---|---|---|
| Age of mother | Pearson Correlation | -0.098 |
| | P-value | 0.256 |
| | Sample size | 143 |

NH is accepted- there is no relationship between the two variables. This weak negative relationship is displayed in Figure 3.10 below.

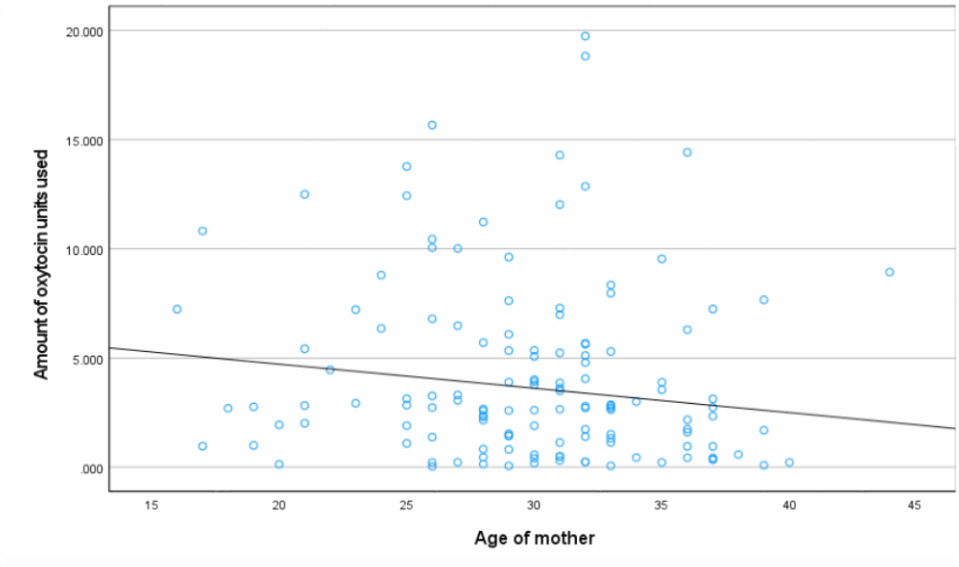


**Figure 3.10:** Amount of OT units used against maternal age

### 3.3.10 Correlating OT units with OT indication

**Table 3.10:** OT units with OT indication

| One-Way ANOVA | | | | | | |
|---|---|---|---|---|---|---|
| | Sample size | Mean | Std. Deviation | p-value | 95% Confidence Interval for Mean amount of OT units used | |
| | | | | | Lower Bound | Upper Bound |
| Induction | 74 | 4.635 | 4.283 | 0.167 | 3.642 | 5.627 |
| Augmentation | 69 | 3.68 | 3.867 | | 2.755 | 4.613 |
| Total | 143 | 4.18 | 4.101 | | 3.498 | 4.854 |

NH accepted-Mean amounts for OT units administered to do vary significantly with OT indication. This is shown in Figure 3.11 below.

The error bar graph shown in Figure 3.11 below shows the 95% CI of the actual mean amount if OT units used for both indications. The overlap of the two CI's indicate that the 2 mean amounts of OT units used for induction and augmentation of labour do not differ significantly.

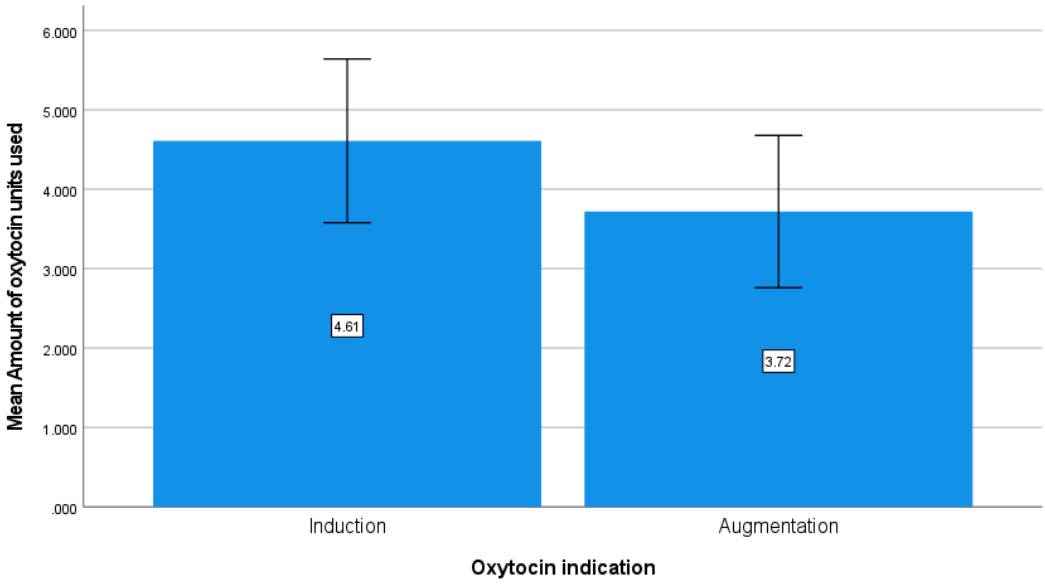


**Figure 3.11:** Mean Amount of OT units used against OT indication

### 3.3.11 Correlating Duration of Labour with prostin administration before OT

**Table 3.11:** Duration of Labour with prostin administration before OT

| One- Way ANOVA | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% Confidence Interval for Mean Duration of Labour | |
| | Sample size | Mean Duration of Labour (1st and 2nd stage) | Std. Deviation | p-value | Lower Bound | Upper Bound |
| yes | 46 | 6.56 | 3.091 | 0.164 | 5.645 | 7.481 |
| no | 95 | 5.71 | 3.515 | | 4.997 | 6.430 |
| Total | 141 | 6.00 | 3.395 | | 5.425 | 6.556 |

NH is accepted- the mean scores vary marginal between the groups. This relationship is displayed in Figure 3.12 below.

The error bar graph (Figure 3.10) below shows this further through the overlap of the two CI's, which imply that the two means do not differ significantly.

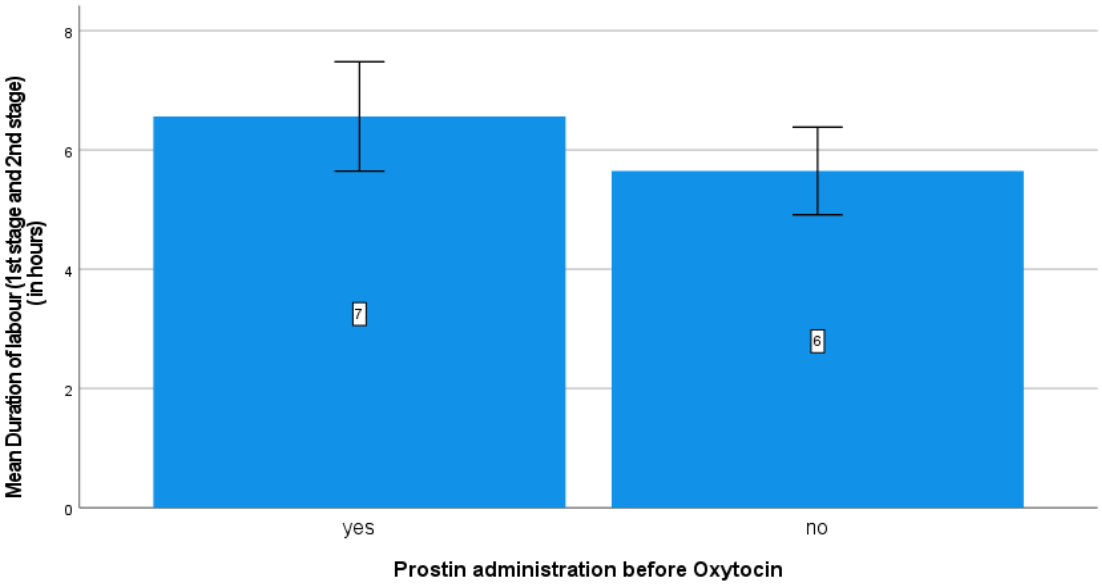


**Figure 3.12:** Mean Duration of Labour (1st and 2nd stage) against prostin administration before OT

### 3.3.12 Correlating OT units with prostin administration before OT

**Table 3.12:** OT units with prostin administration before OT

| One-Way ANOVA | | | | | | |
|---|---|---|---|---|---|---|
| | Sample size | Mean Amount of OT units used | Std. Deviation | p-value | 95% Confidence Interval for Mean Amounts of OT units used | |
| | | | | | Lower Bound | Upper Bound |
| yes | 46 | 3.73 | 3.213 | 0.460 | 2.760 | 4.690 |
| no | 95 | 4.28 | 4.428 | | 3.370 | 5.174 |
| Total | 141 | 4.096 | 4.073 | | 3.416 | 4.777 |

NH accepted-mean scores vary marginal between the groups. This is displayed in Figure 3.13 below.

The error bar graph below display the 95% CI's of the actual mean amounts of OT units administered when prostin was used and not used. The overlap of the two CI's also indicates that the mean amounts do not differ significantly.

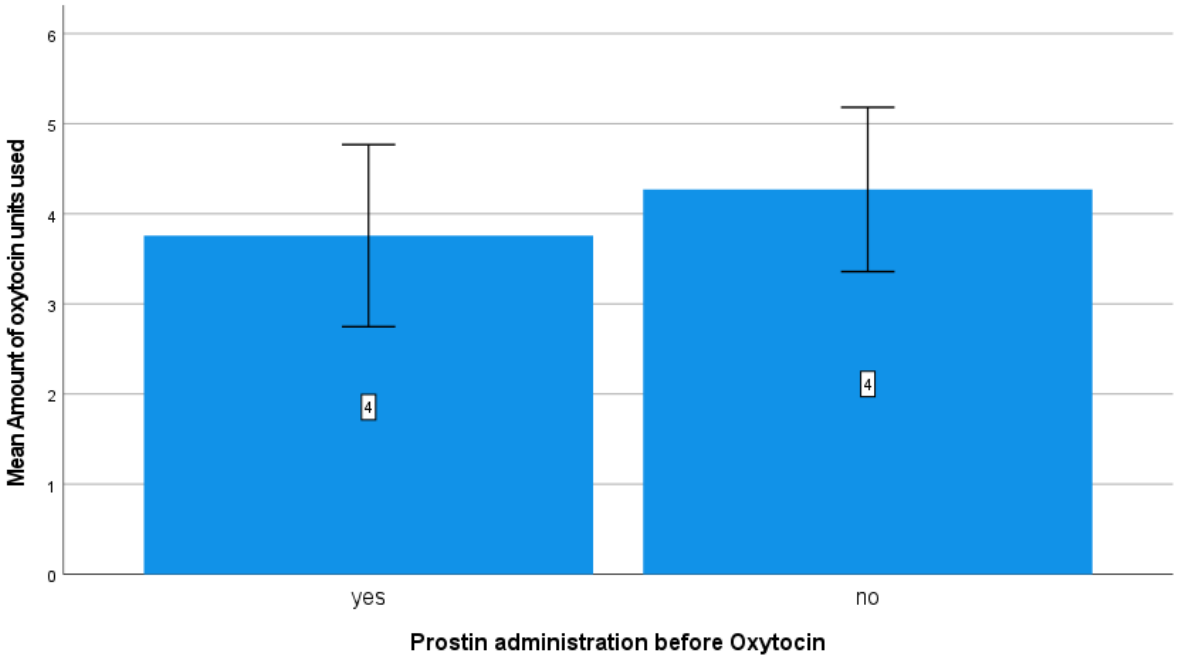


**Figure 3.13:** Mean amount of OT units used against prostin administration before OT

### 3.3.13 Correlating OT use with prostin use

**Table 3.13:** OT use with prostin use

| Chi-Squared | | | | | |
|---|---|---|---|---|---|
| | | | Prostin administration before OT | | |
| | | | Yes | No | Total |
| Was oxytocin used? | Yes | Count | 46 | 94 | 140 |
| | | Percentage | 100.0% | 98.9% | 99.3% |
| | No | Count | 0 | 1 | 1 |
| | | Percentage | 0.0% | 1.1% | 0.7% |
| Total | | Count | 46 | 95 | 141 |
| | | Percentage | 100.0% | 100.0% | 100.0% |

$X^2(1) = 0.488$, $p = 0.485$

The NH is accepted-no significant association between the two variables. This is displayed in Figure 3.14 below.

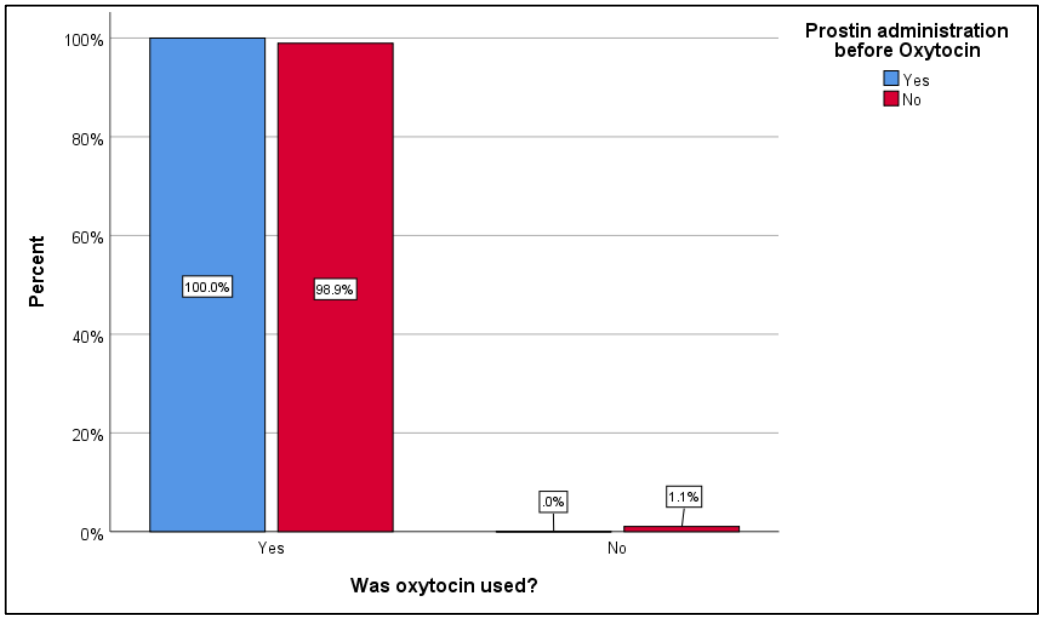


**Figure 3.14:** Prostin use against OT use

### 3.3.14 Correlating Amount of OT unit used with time taken to reach maximum dilation (10cm)

**Table 3.14:** Amount of OT used with First stage duration

| Pearson Correlation | | |
|---|---|---|
| Amount of oxytocin units used | Pearson Correlation | 0.427 |
| | P-value | 0.000 |
| | Sample size | 136 |

AH is accepted i.e. there is a significant relationship between the two variables. This is shown in Figure 3.15 below.

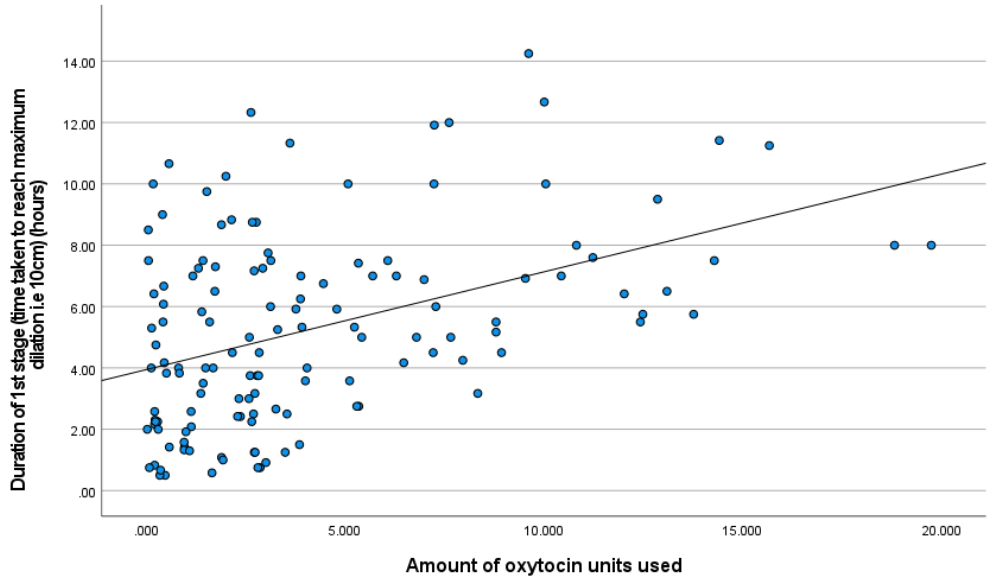


**Figure 3.15:** Duration of labour (1st and 2nd stage) against Amount of OT units used

### 3.3.15 Correlating OT units used with parity

**Table 3.15:** OT units with parity

| Pearson Correlation | | |
|---|---|---|
| Amount of oxytocin units used | Pearson Correlation | -0.167 |
| | P-value | 0.052 |
| | Sample size | 136 |

NH accepted- there is no relationship between the two variables. This negative relationship is displayed in the scatter plot below (Figure 3.16).

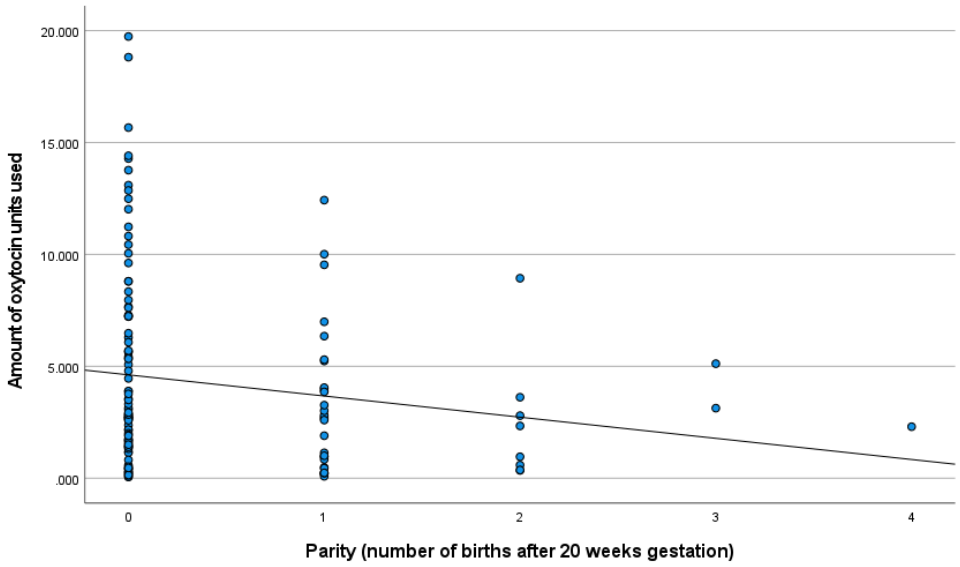


**Figure 3.16:** Amount of OT units used against Parity

### 3.3.16 Correlating duration of Labour with Parity

**Table 3.16**: Duration of Labour with Parity

| Pearson Correlation | | |
|---|---|---|
| Duration of labour (1st stage and 2nd stage) ( in hours) | Pearson Correlation | -0.289 |
| | P-value | 0.000 |
| | Sample size | 250 |

AH accepted-there is a significant association between the two variables. Figure 3.17 below shows this relationship.

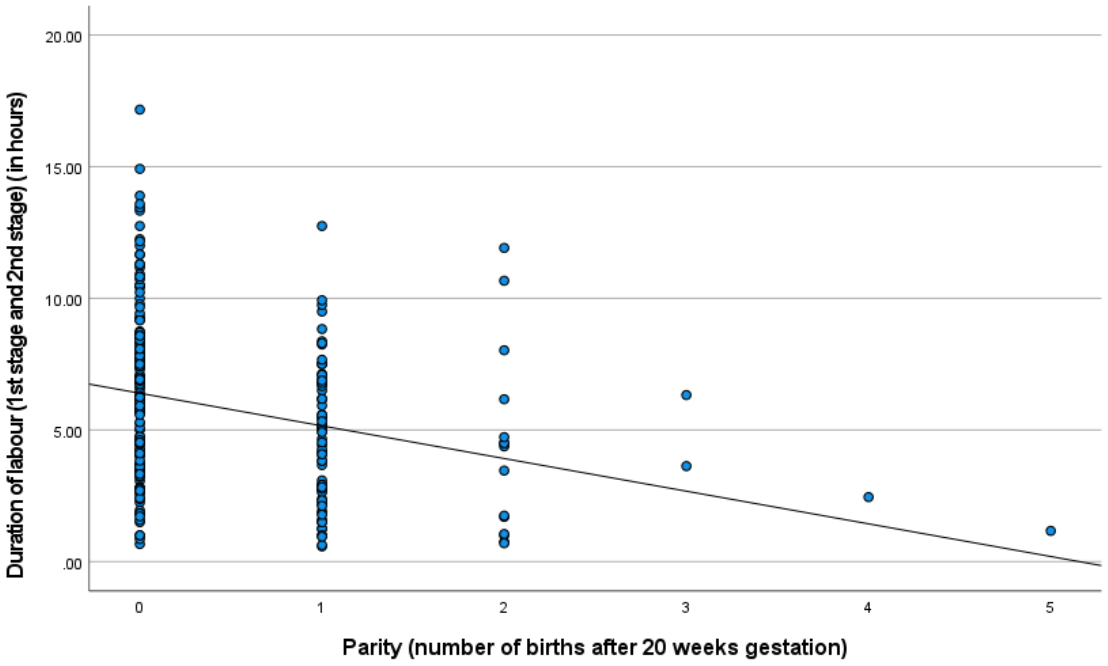


**Figure 3.17:** Duration of Labour against Parity

### 3.3.17 Correlating OT units administered with gestational age

**Table 3.17:** OT units with gestational age

| Pearson Correlation | | |
|---|---|---|
| Amount of oxytocin units used | Pearson Correlation | 0.060 |
| | P-value | 0.483 |
| | Sample size | 139 |

NH is accepted- there is no relationship between the two variables. The scatter plot below (Figure 3.18) displays this relationship.

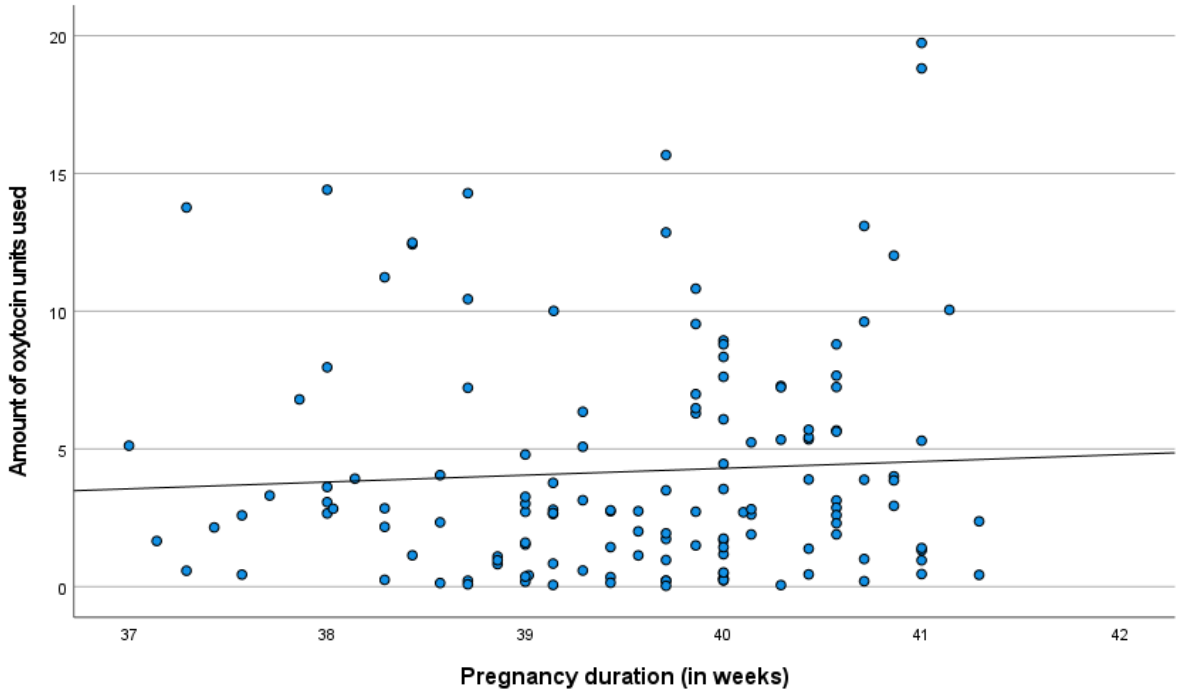


**Figure 3.18:** Amount of OT units used against gestational age

### 3.3.18 Correlating Bishop Score with amount of OT units used

**Table 3.18:** Bishop Score with OT units

| Pearson Correlation | | |
|---|---|---|
| Amount of oxytocin units used | Pearson Correlation | -0.017 |
| | p-value | 0.842 |
| | Sample size | 143 |

NH accepted-there is no relationship between the two variables. This weak relationship is displayed in the chart below (Figure 3.19) below.

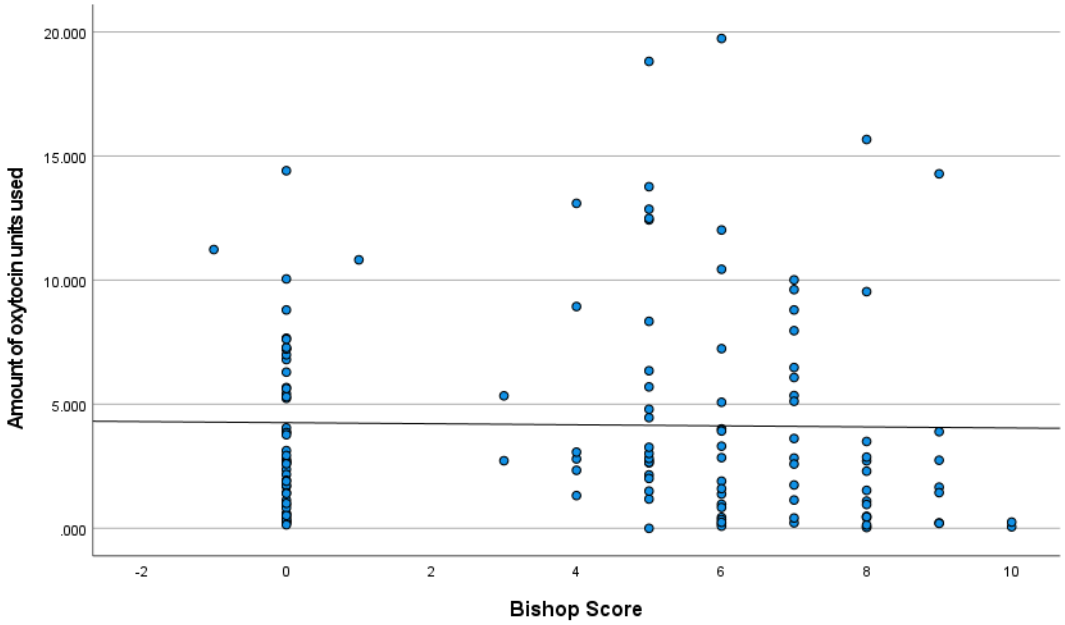


**Figure 3.19:** Amount of OT units used against Bishop Score

### 3.3.19 Correlating Duration of second stage of Labour with OT units

**Table 3.19:** Duration of Second stage of Labour with OT units used

| Pearson Correlation | | |
|---|---|---|
| Amount of oxytocin units used | Pearson Correlation | 0.384 |
| | p-value | 0.000 |
| | Sample size | 143 |

AH accepted- there is a significant relationship between the two variables (Table 3.24).

This is displayed in Figure 3.20 below.

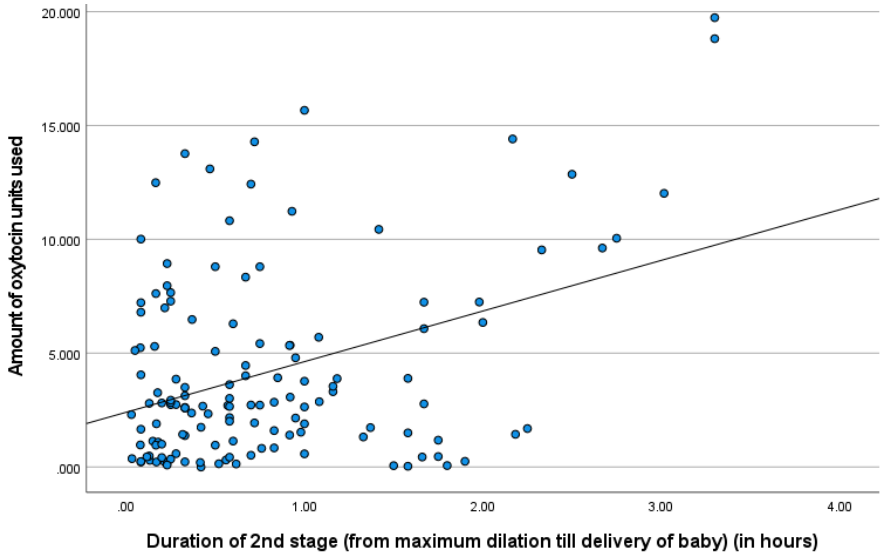


**Figure 3.20:** Amount of OT units used against Duration of second stage of Labour

### 3.4 Local OT Protocol- Labour Ward Management of High risk Pregnancies and Abnormal Labour

Although there was a general acknowledgement that a printed marker protocol exists for use of OT, and protocol was accessible, it was observed that few made direct use of the document.

As per the two-page current local OT protocol followed at MDH, OT is indicated for the acceleration of dysfunctional labour, after membranes have been ruptured naturally or artificially. OT is administered via IV infusion containing 10 units of OT in 500 mL of normal saline. In normal singleton pregnancies, the infusion is started at 6 mL/hr and may be doubled every 15 minutes if needed up to a maximum of 96 mL/hr or until established contractions are reached. In particular scenarios like twin pregnancies, grand multis and mothers with a previous CS, the OT infusion should be used with great caution. The starting infusion rate is 3 mL per hour which may be doubled, if necessary every 30 minutes (Mater Dei Hospital, no date). The protocol also states that Continuous Foetal Monitoring is to be done whenever OT is administered to allow for early detection of hyperstimulation and/or foetal distress. The use of OT infusion during labour is contraindicated in hypertonic uterine contractions, in mechanical obstruction to delivery, in failed trial of labour – Cephalopelvic disproportion, in foetal distress and in placenta praevia ( when the placenta grows at the cervical opening, covering parts or all of it).[11] Adverse effects listed include uterine hypertonus and water intoxication, which may manifest itself as headache, nausea, vomiting, anorexia,

[11] MedlinePlus. Placenta Previa [Internet]. US: US National Library of Medicine; 2020[cited May 11 2020]. Available from: https://medlineplus.gov/ency/article/000900.htm

abdominal pain, lethargy, drowsiness, unconsciousness and seizures.[12] It is also noted that OT is inactivated by oxytocinase so it cannot be administered through the same line as blood or plasma.

### 3.5 Adherence to local protocol

In 11 out of the 143 cases where OT was used, the local protocol was not precisely followed, making up 7.7% of the OT group. Three cases were augmented VBACs and eight were NVDS, 5 inductions, 1 of which was delivered by ventouse due to foetal distress and 3 augmentations, including one grand multip (P=4+0).

Two of the VBACs did not follow protocol in the way that the infusion rate was started at 6 mL/hr, rather than at 3 mL/hr, as stated in the protocol. The other VBAC case deviated from protocol as the infusion rate was doubled sooner than after 30 minutes, specifically after 20 minutes. The remaining eight deviations resulted from doubling the infusion rate after 10 minutes instead of after 15 minutes for normal pregnancies, and sooner than after 30 minutes for the grand multip, specifically after 15 and 20 minutes.

Following the calculation described in section 2.10, it was found that in 6 cases from a total 140 cases (3 had missing data) the OT units used were higher than the maximum units according to the local protocol. This amounts to 4.3% of the OT group. The OT units used in the other 134 cases were within range of the local OT protocol.

### 3.6 NPICU admissions

Five NPICU admissions were identified in all. All of these admissions occurred following OT use; 1 following Em/LSCS, 3 following OT induction (1 of which was ventouse

[12] Electronic Medicines Compendium (eMC). Oxytocin 10 IU/ml Solution for infusion - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd.; 2019 [cited 17 May 2020]. Available from: https://www.medicines.org.uk/emc/product/9334/smpc

delivery) and 1 following OT augmentation. This finding therefore presents a positive correlation between OT use and NPICU admission.

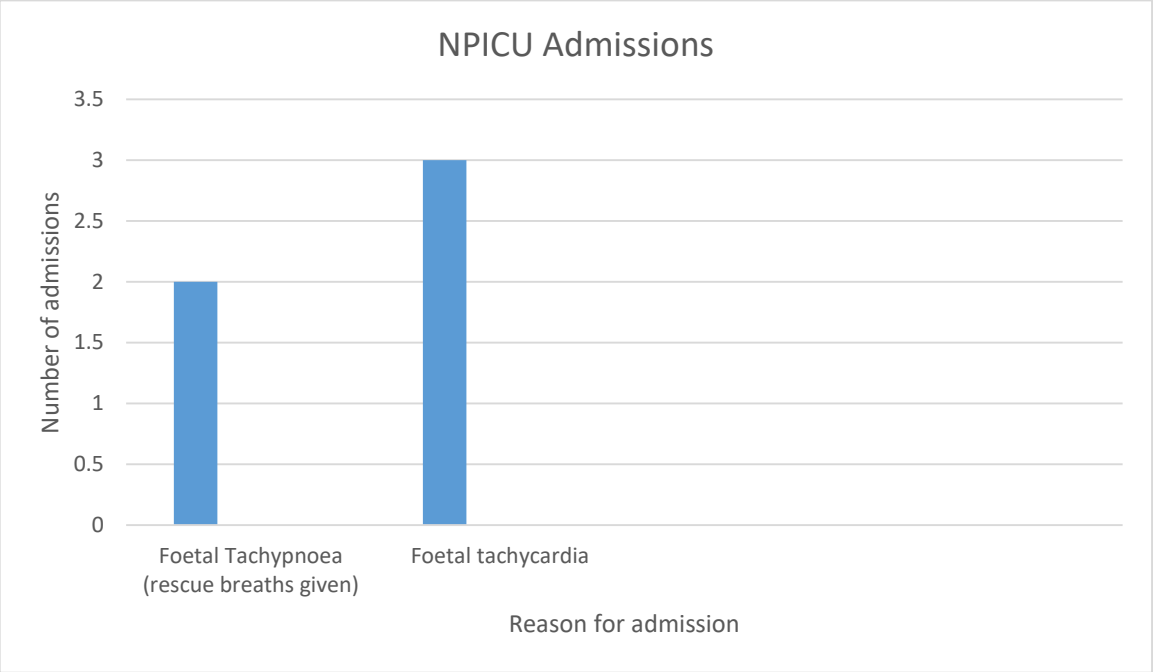


**Figure 3.21:** Number of NPICU admissions against reason for admission (N=5)

### 3.7 Emergency Low Segment Caesarean Sections

33 Em/LSCS cases were performed; 14 following no OT use and 16 following OT use, 4 after OT induction and12 following OT augmentations.

1 breech case, where no OT was administered was delivered by Em/LSCS.

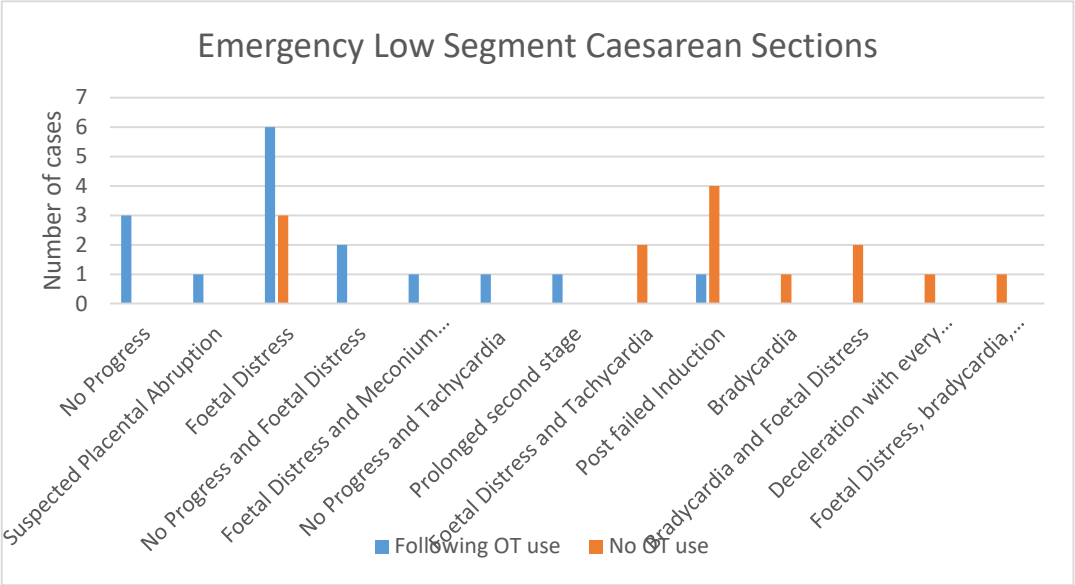


**Figure 3.22:** Number of births delivered by Em/LSCS against reason for Em/LSCS (N=33)

### 3.8 Local Protocol vs International guidelines

The current local protocol and the international guidelines reviewed (Table 3.24) all included OT indications, contraindications cautions and adverse events. The infusion concentration, initial and maximum infusion rates were not consistent, though similar. Although not all, some of the international guidelines included how to go about the event of uterine tachysystole including the use of particular drugs such as terbutaline. Following discussion with an obstetrician at MDH, it was learnt that terbutaline is not available on labour ward; but salbutamol is, which is also used as a tocolytic. The local protocol does not differentiate between initial and maximum infusion rates for

nulliparous and multiparous women. This difference was documented in one and three of the reviewed international guidelines.

**Table 3.20:** Local Protocol vs international guidelines

| OT administration Guideline | Mater Dei Hospital, Malta | Alberta Health Services, Canada | ACOG Practice Bulletin | Government of South Australia | Bolton, NHS Foundation Trust | Wrightington, Wigan and Leigh, NHS Foundation Trust | Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and the Clinical Strategy and Programme division, Health Service Executive | Auckland District Health Board, New Zealand | Tameside Hospital, NHS Foundation Trust |
|---|---|---|---|---|---|---|---|---|---|
| **Preparation of Infusion** | 10 u in 500 mL normal saline | 20 u. in 1000 mL normal saline or ringer's lactate solution | Generally 10 u. in 1000 mL 0.9%NaCl | 10 u in 1000 mL of Hartmann's solution or sodium chloride 0.9% | 30 u in 500 mL 0.9% NaCl | 10 u in 1000 mL normal saline | 10 u in 1000 mL of 0.9 % normal saline | 10 u in 500 mL 0.9% NaCl | 10 u in 500 mL normal saline |
| **Starting dose** | 6 mL/hr | 1-2 mu/min i.e. 3 mL-6 mL/hr | Low-dose; 0.5-2mU/min High-dose-6mU/min | 2 mu/min= 12 mL/hr | 2 mL/hr=2 mu/min | 10 mL/hr=1.7 mU/min | 1-5 mU/min= 6-30 mL/hr | 6 mL/hr=2 mU/min | 3 mL/hr |
| **Maximum dose** | 96 mL/hr | 20 mu/min i.e. 60 mL/hr | Not established | 192 mL/hr=32 mu/min | Multiparous :16 mL/hr 32 mL/hr where effective contractions not reach at max dose<br>Nulliparous: 32 mL/hr 48 mL/hr where effective contractions not reach at max dose | 70mL/hr 11.9 mU/min<br>Higher doses might be used; 120 mL/hr=20.4 mU.min | 30 mU/min= 180 mL/hr | 96 mL/hr=32 mU/min | 60 mL/hr Higher doses 72 mL/hr to 96 mL/hr upon registrar approval |
| **dosage regimen** | Double every 15 minutes in certain situation, start at 3 mL/hr and double every 30 | Increase at 1-2 mu/min every 30 mins | For High-dose regimen-increments of 3-6 mU/min every 15-40 min; low-dose 1-2 mU/min every 15-40 min | Increase at 12 mL/hr (2 mU/min) every 30 minutes | Increase by 4 mL/hr every 30 mins | Increase by 10 mL/hr =1.7 mU/min every 30 mins | 1-5 mU/min (6-30 mL/hr every 15-30 min | For 6 mL/hr to 24 mL/hr increased by 6 mL/hr; for 36 mL/hr to 84 mL/hr increase by 12 mL/hr every 30 mins | For 3 mL/hr - 12 mL/hr rate is doubled every 20 to 30 minutes; for 24 mL/hr to 84 mL/hr increase by 12 mL/hr |

# CHAPTER 4

# DISCUSSION

This chapter will focus on discussing the results obtained from this. Study limitations and recommendations for future studies will be outlined. The importance of having the Pharmacist forming an integral part of the interdisciplinary team in this speciality will be described. Conclusions will be drawn out at the end, aiming to optimise the practice in the field.

### 4.1 Local Practice

Disparities from the local protocol (described in section 3.5) pertaining to sooner than recommended rate doubling and higher than recommended initial infusion rates were observed in 7.7% of the OT group. Although there appears to be no specific clinical justification for such deviations, one would need to analyse the individual cases in greater depth and look at the respective patients' notes for possible explanations. With regard to vaginal birth after caesarean section, a new protocol has been issued for this occurrence during the time of dissertation writing, so this could be a possible area of interest for future studies.

The 4.3 % deviation described in section 2.10 i.e. maximum recommended OT units as per protocol versus actual amount of OT administered, presents another deviation. The amount of OT units used in these reviewed cases was higher than the maximum recommended amount defined in the local protocol i.e. 10 IU in 500 mL. Such higher than recommended usage could be justified by specific clinical reasons, the identification of which fell beyond the scope of this study. The 4.3% deviation from the local protocol may be regarded as a relatively low figure. However when one considers deviation from the respective SPC, the situation is such that the protocol itself recommends an off-licence dose since the Summary of Product Characteristics of Syntocinon® recommends that 5 IU are mixed with 500 mL of electrolyte solution and

that 10 IU per 500 mL are only advised in cases of in-utero foetal death and labour induction earlier in pregnancy. The average gestational age in the investigated group in this study was 39.35 weeks. Consequently the SPC indication regarding labour induction in earlier pregnancy is not applicable. It must be highlighted that such off-licence recommendation is evident in other reviewed international guidelines. This indicates the need for further clinical studies and evaluation in order to update respective protocols and/or product market authorisation in order to standardise the use of OT.

In cases of tachysystole and change in FHR patterns, the infusion rate of OT was observed to be adjusted at lower rates or stopped altogether. The one breech case encountered in this study, was delivered by Em/LSCS, rather than by El/LSCS. In spite of the limited number of opportunities to come across such occurences, this still emphasises the importance of reviewing current local protocols pertaining to breech presentations, as highlighted by Fenech and Grech (2020).

An updated, possibly more detailed version of the local OT protocol could be issued and made more accessible to all respective HCPs. A number of patient files had missing data. This might have been a result of such data being documented elsewhere in the patient file or not being documented at all. This point reminds us of the importance of systematic documentation and filing, about which more awareness should be made. This would not only facilitate necessary documentation by HCPs on the ward, but also avoids the occurrence of any potential associated errors. Perhaps a more appropriate way forward would be through the use of drug order sets, specific to the use of OT (ISMP, 2020).

### 4.2 Maternal and foetal outcomes

The AS at 5 minutes was not found to be significantly less with OT use, however other studies documented a significant correlation of a 5 minute AS less than 7 with OT use (Oscarsson et al., 2006).

A significant difference in the mean ASs at 1 minute with a prolonged second stage of labour is in line with the findings of Altman et al. (2015). Mothers in such cases may or may not have used OT, which in turn could have contributed to the prolongation of the second stage of labour.

The mean duration of the first stage of labour has been shown to be significantly longer with more OT units used. This positive correlation could be explained by the notion that if the mother is administered more OT, the contractions have not yet reached the expected level of intensity and/or frequency. This leads to a longer first duration of labour. This finding however is not consistent with the findings of other authors including Zhang et al. (2011) and Hidalgo-Lopezosa et al. (2016) who reported a significantly shorter first stage of labour when higher doses of OT were used (initial infusion rate of 4mU/min and increasing by 4mU/min).

In the current study the mode of delivery following OT use did not vary significantly with the mode of delivery of the control group. This finding differs from the results of other studies including Tesemma et al. (2020). There was a statistical significance of a longer second stage of labour with a higher incidence of ventouse delivery. The duration of labour was shown to be significantly shorter for women with more parity. This finding is supported by Selman and Johnston (2013) who deduced that the first stage of labour for nulliparous women lasts between eight and eighteen hours on average, while for multiparous mothers, the first stage lasts from five to twelve hours.

The second stage of labour is reported to be about 3 hours for nullipara and 2 hours for multipara (Selman and Johnston, 2013).

The fact that NPICU admissions in this study all occurred following OT use, it cannot be concluded that this was a result of OT administration, keeping in view the presence of other confounding factors. However it emphasises the need to adopt a standardised approach towards OT use and to investigate further the influence of OT on neonates. The same applies for the occurrence of Em/LSCS. The rationales behind Em/LSCS being performed following OT use is not necessarily precipitated by OT use, but literature does show a significant positive correlation (Krening et al., 2012).

### 4.3 Clinical Pharmacy

The approach towards having a specialised Pharmacist forming an integral part of the inter-disciplinary, direct-patient care team has been globally increasing, a concept which is also supported by the ACOG. The Pharmacist's active contribution safeguards the patient's health through the practice of Comprehensive Medication Management (CMM), enabling the optimal use of medications (American College of Clinical Pharmacy, 2014; Jacobi, 2016), with more emphasis on treating the patient and not the condition. In his article Briggs (2018) reports the low involvement of Pharmacists in obstetric care, a participation which had been proven to positively affect both mother and neonate.

In obstetrics, the use of OT is just one pharmaceutical issue. Anaesthesia, the use of analgesic agents together with any long-term maternal co-morbidities such as diabetes and hypertension are other areas where Pharmacists' interventions are fundamental. A Pharmacist specialised in obstetrics can implement systematic changes, one of which is drug order sets, with the aim of improving patient care through the standardisation

of the best evidence-based practices (Cohen and Sanborn, 2008). The statistically significant shorter duration of labour with higher parity is consistent with findings from other authors (Selman and Johnston, 2013).

### 4.4 Limitations

This study focused on the evaluation of OT use in Malta's main acute hospital, i.e. MDH. Private hospitals were not taken into consideration. Since most specialists practicing at MDH also attend at private settings, it is most likely that similar protocols are followed. However this cannot be confirmed unless similar studies in such institutions are carried out.

Another limitation of this study regards the use of other pharmaceuticals during labour besides OT. Such drugs include analgesics which can be administered in various dosage forms including EDA. As explained in chapter two, EDA prolongs the second stage of labour (Shmueli et al., 2018), which translates into an overall longer duration of labour. If mothers included in this study were administered both EDA and OT, which have been shown to be significantly associated with each other due to less sensation during labour when EDA is administered, (Shmueli et al., 2018), it follows that their respective duration of labour was potentially influenced by EDA. However it is difficult to deduce an interpretation of the result due to the presence of confounding factors.

Scientific literature and practice guidelines researched for this study were limited to the English language. There may be several other relevant references in other languages that could provide further insight of what practice approaches are followed internationally.

### 4.5 Recommendations

Findings of this study support the growing belief that OT should not be used routinely during labour, but reserved specifically to situations where OT is indicated to protect maternal and foetal well-being. This logic pertains not only to the relatively short term effects observed during labour, but also to potential effects that might come up later in life. There seems to be no universal agreement in scientific literature on the most suitable OT dosing regimen that best safeguards maternal and foetal well-being. More studies are required to better evaluate the use of OT and its effects, addressing also the concept of OT discontinuation once established labour is reached, which is supported by the study conducted by Daniel-Spiegel et al. (2004), with no labour prolongation.

Since evaluations for the study did not make use of partograms, occurrences of utrine hyperstimulation could not be investigated. This could be an aspect for future studies for deeper understanding of the actions of OT. Evaluating CTG enables the identification of uterine tachysystole and FHR patterns during OT administration. Taking cord blood samples to evaluate for acidaemia is another aspect one could correlate with OT use together with the mother's fluid intake during OT administration to investigate the water intoxication adverse effect of OT. The use of OT in specific patient populations including diabetic and hypertensive mothers could also be a possible subject for future research. High dose and low-dose OT regimen protocols should be investigated further with the aim of finding the best evidence-based OT regimen. These elements could lead to a deeper understanding of the actions of OT within an actual clinical environment.

### 4.6 Conclusion

The benefits of OT during parturition cannot be underestimated. However, this high-alert drug must be used with great caution to prevent any adverse outcomes on mother and neonate, which outcomes can occur during labour itself or later in life. Respective HCPs must be updated on any emerging evidence on OT to be better equipped to educate the parturient about OT and the associated risks, both immediate and delayed. This will facilitate both HCPs and respective mothers to make informed decisions on Syntocinon® administration for best possible outcome (Khajehei, 2017).

Optimising OT use during labour should be the common goal of all HCP stakeholders aiming at maintaining maternal and foetal well-being and making the birth experience a positive one for all those involved.

A risk-benefit assessment should be carried out before deciding to initiate OT administration and strategies must be in place to reduce the associated maternal and foetal risks as much as possible. This study gives a snapshot of local obstetric practice pertaining to OT use at MDH. Further studies are suggested to investigate the actions of OT with the aim of reaching the implementation of the standardised use of this high-alert drug. One such study would be the evaluation of the clinical studies pertaining to the market authorisation of Syntocinon® and equivalent products and to analyse why several protocols including the local one, differ from the respective SPCs. This study shows that there is no general consensus on the optimum dose of OT for induction or augmentation of labour, both at the national and international level. It was also observed that there are substantial differences between the various protocols evaluated, in particular with respect to the maximum recommended dose of OT and dosage regimen. Such lack of consensus may be attributed to intra and inter clinical

disagreement between HCPs, namely obstetricians and midwives / specialised nurses. An approach aimed at addressing such practice variation is to have active involvement of the Pharmacist who would be in an ideal position to coordinate the use of appropriate checklists. Such checklists may take the form of pre and in-use checklists which would facilitate collaborative clinical decision making prioritising patient safety (Clark et al., 2017). Furthermore, the use of drug order sets would facilitate a standardised treatment approach thereby minimising potential prescribing and drug administration errors (ISMP, 2020). In such situations it would be of value that Pharmacy co-ordinates an interdisciplinary group of the requisite stakeholders in the drafting, implementation, monitoring and continuous updating of relevant clinical practice guidelines, ensuring effective adherence to evidence based practice.

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**APPENDICES**

**Appendix 1:** Checklist used during data extraction

| **Factors** | **Data** | | |
|---|---|---|---|
| Date of data collection | | | |
| Age of the mother | | | |
| Nulliparous or multiparous | | | |
| If multiparous, were previous births delivered normally or by C-section | | | |
| After how many weeks into pregnancy did the mother come to MDH Obstetrics and Gynaecology unit | | | |
| Was Oxytocin used | | | |
| If Oxytocin was used; for how many hours | | | |
| Was Oxytocin used for induction or augmentation of labour | | | |
| Amount of OT units administered | | | |
| Duration of Labour $1^{st}$ stage,$2^{nd}$ stage, $1^{st}+2^{nd}$ | | | |
| Was delivery following Oxytocin use normal, aided with forceps or C-section | | | |
| Apgar score- at 1 minute and at 5 minutes | | | |

**Appendix 2:** How to Calculate OT units administered

For example; if a mother was administered OT infusion at 6 mL/hr for 15 minutes;

10 units in 500 mL

? in 6 mL

(10x6) /500= 0.12 units OT

0.12 units OT in 60 minutes

? in 15 minutes

(0.12x15)/60 = **0.03 OT units**

**Appendix 3:** Local OT protocol

## LABOUR WARD MANAGEMENT OF HIGH RISK PREGNANCIES AND ABNORMAL LABOUR

**General Comments**

- The antenatal identification and clear labeling of any risk factors. The Management plan during labour has to be clearly spelt out in the case notes with appropriate identification of the authorising person.
- Good communication with the patient and partner as well with professional colleagues, anticipation and early detection of problems with prompt and appropriate action.
- The lines of communication have to be well-recognised in emergencies.
- Complete the appropriate details in the Labour Ward Delivery Register

## ACCELERATION OF DYSFUNCTIONAL LABOUR

- In low risk primigravida patients with dysfunctional labour, a decision to commence syntocinon is a medical one. The decision to use oxytocin in any high risk patient must be taken by a registrar or above.

- Syntocinon must not be used when a secondary arrest of labour has occurred (i.e. failure of dilation at or after 6 – 7cm) until obstructed labour has been excluded by the on call Registrar.

- **SYNTOCINON IS NOT RECOMMENDED UNTIL MEMBRANES ARE RUPTURED.**

- In a multiparous patient, augmentation needs to be commenced only after assessment by the Registrar. Annotation to this effect must be made by the Obstetric Registrar in the case notes.

**SYNTOCINON INFUSION**

**Syringe Pump**

- Ten (10 units) of Syntocinon to be mixed with 500ml of normal saline through IVAC pumps. This infusion is started at 6ml per hour and doubled quarter hourly until regular contractions are established or to a maximum of 96 ml/hour.

- In certain situation, i.e. twin pregnancy, multiparous patients especially grand multis and those with a previous Caesarean section, Syntocinon should be used with great caution and needs to be increased every half hour starting at 3 mls/hr (i.e3, 6, 12, 24, 48, & 96 ml/hour maximum dose)

**Professor Lilian M. Azzopardi**
B.Pharm.(Hons.),M.Phil. Ph.D. MRPharmS
Head, Department of Pharmacy
Faculty of Medicine & Surgery
University of Malta

## SYNTOCINON INFUSION

| Ml/hour | units/hour | micro | units/min |
|---|---|---|---|
| 6mls/ hr | 12u | or | 2microu |
| 12ml/hr | 24u | or | 4microu |
| 24ml/hr | 48u | or | 8microu |
| 48mls/hr | 96u | or | 16microu |
| 96 mls/hr | 192u | or | 32microu |

- CONTINOUS FHR MONITORING whenever syntocinon infusion is used.
- Any evidence of excessive uterine contractions and/or significant bradycardia – stop syntocinon and call the Registrar.

## OXYTOCIN (SYNTOCINON ® SANDOZ)

Administered by intravenous infusion.

As labour becomes established, the uterus becomes more sensitive to oxytocin (usually from about 5cm dilation).

### Principles of Oxytocin regime:

- Initially given in low doses
- Gradually and steadily increased until effective contractions are produced
  - The dose rate is varied to suit the individual patient : aim to detect any hyperstimulation early

**Contra- indications**
- Hypertonic uterine contractions
- Mechanical obstruction to delivery
- Failed trial of labour – established CPD
- Fetal distress
- Placenta praevia

*Precautions*
- Multiple pregnancy
- High parity
- Previous Caesarean section
- Action may be potentiated by prostaglandins

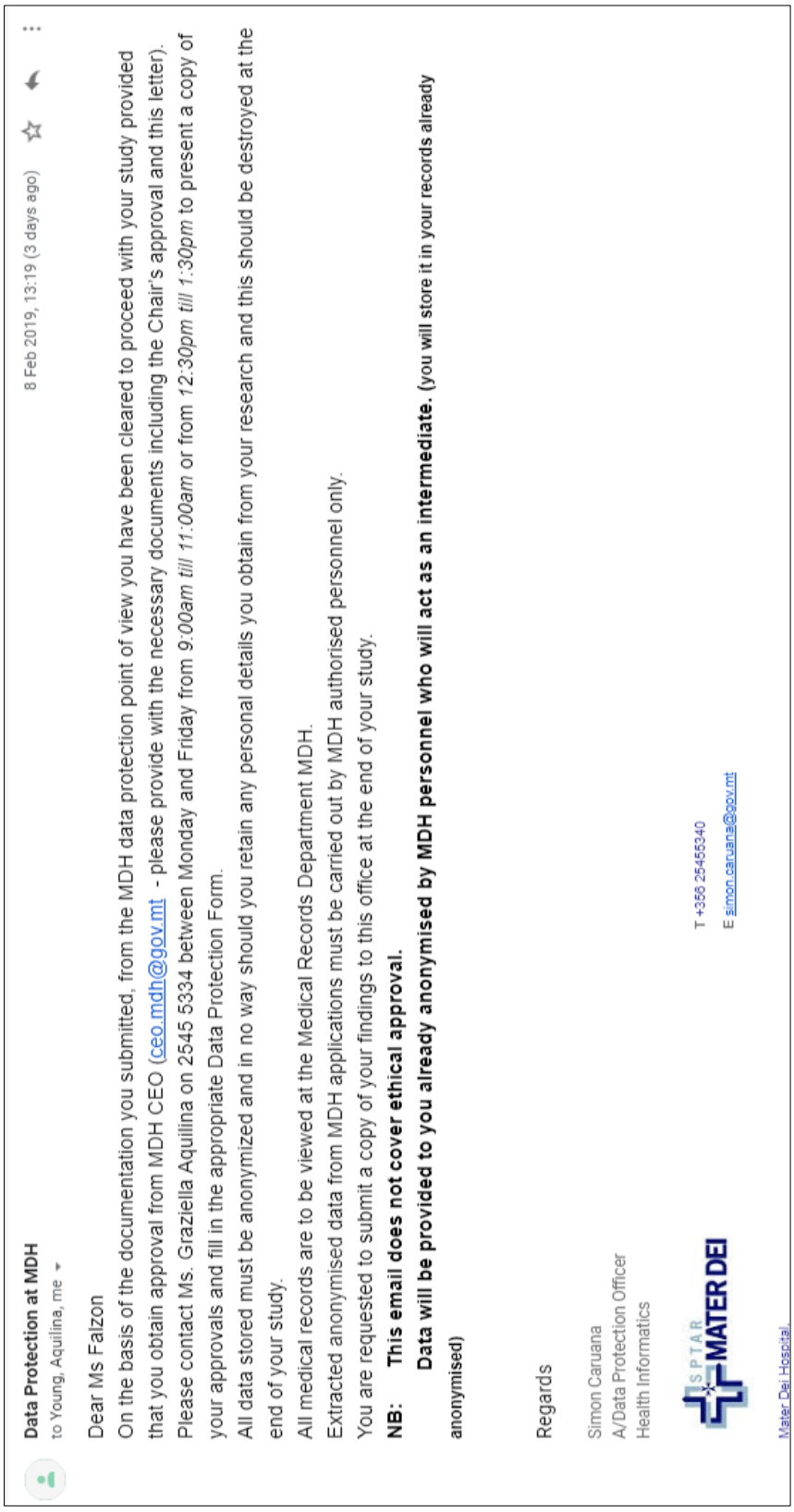
*Side Effects*
- Uterine hypertonus
- Water intoxication – headache, anorexia, nausea, vomiting, abdominal pain, lethargy, drowsiness, unconsciousness, seizures

*Note:*
Cannot be infused through the same line as blood or plasma – inactivated by oxytocinase.

**Professor Lilian M. Azzopardi**
B.Pharm.(Hons.),M Phil.,Ph D., MRPharmS
Head, Department of Pharmacy
Faculty of Medicine & Surgery
University of Malta

**Appendix 4:** Approvals

**Appendix 4.1:** Approval from Chief Executive Officer MDH



**Data Protection at MDH** 8 Feb 2019, 13:19 (3 days ago)

to Young, Aquilina, me

Dear Ms Falzon

On the basis of the documentation you submitted, from the MDH data protection point of view you have been cleared to proceed with your study provided that you obtain approval from MDH CEO (ceo.mdh@gov.mt - please provide with the necessary documents including the Chair's approval and this letter).

Please contact Ms. Graziella Aquilina on 2545 5334 between Monday and Friday from *9:00am till 11:00am* or from *12:30pm till 1:30pm* to present a copy of your approvals and fill in the appropriate Data Protection Form.

All data stored must be anonymized and in no way should you retain any personal details you obtain from your research and this should be destroyed at the end of your study.

All medical records are to be viewed at the Medical Records Department MDH.

Extracted anonymised data from MDH applications must be carried out by MDH authorised personnel only.

You are requested to submit a copy of your findings to this office at the end of your study.

**NB: This email does not cover ethical approval.**

**Data will be provided to you already anonymised by MDH personnel who will act as an intermediate.** (you will store it in your records already anonymised)

Regards

Simon Caruana
A/Data Protection Officer
Health Informatics

T +356 25455340
E simon.caruana@gov.mt

Mater Dei Hospital

**Appendix 4.1:** Approval from Data Protection Officer MDH



CEO at MDH
to me
12:36 (10 minutes ago)

Dear Ms Falzon,

Please note that Mr Ivan Falzon has granted approval for you to conduct this study in line with applicable hospital protocols.

Regards

Carmen Farrugia
Personal Assistant to the CEO
T +356 +356 25454102
E carmen.farrugia@gov.mt
Mater Dei Hospital, Triq Id-Donaturi Tad-Demm, Msida, Malta MSD 2090 | Tel +356 2545 0000 | https://careandcure.gov.mt/

**Appendix 4.3:** Letter to Chairman of Obstetrics and Gynaecology Department and respective Consultants

Data Protection Officer,
Administration Block,
Mater Dei Hospital.

Consultants Obstetrician and Gynaecologist,
Department of Obstetrics and Gynaecology,
Mater Dei Hospital.

19/11/2018

Dear Prof Y Muscat Baron,

I would be grateful if I were allowed to carry out a study entitled "Pharmaceutical Intervention during Labour" within the Department of Obstetrics and Gynaecology

Yours truly,

Ms Rebecca Marie Falzon

Dear Colleagues,

I would be grateful if you were to give your approval for the above mentioned Pharmacy student to undertake this study. The student's supervisors are Prof Lilian Azzopardi and Dr Louise Grech of the Department of Pharmacy University of Malta.

Kind Regards

Prof Yves Muscat Baron

Mr M Formosa

Mr Alberto Vella

Ms Isabelle Saliba

Ms Carmen Portelli

Mr AP Scerri

Mr Johri Thake

Mr Mark Sant

Mr Marcus Pace

**Appendix 4.4:** Approval Letter from Faculty Research Ethics Committee

L-Università ta' Malta

Faculty of
Medicine & Surgery
University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: **FRECMDS_1819_51**

Friday 10th May 2019

Ms Rebecca Marie Falzon
36, Erfolg,
Triq il-Kappar,
Attard. ATD2282.

Dear Ms Rebecca Marie Falzon,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

**Pharmaceutical Interventions during Labour**

The Faculty Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Professor Pierre Mallia
Chairman
Research Ethics Committee