



## European Guidelines on Perinatal Care - Oxytocin for induction and augmentation of



labor

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
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## European Guidelines on Perinatal Care - Oxytocin for induction and augmentation of labor



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### SUMMARY OF RECOMMENDATIONS

1. Oxytocin for induction or augmentation of labor should not be started when there is a previous scar **on the body of the uterus** (such as previous classical cesarean section, uterine perforation or myomectomy when uterine cavity is reached) or in any other condition where labor or vaginal delivery are contraindicated. (**Moderate quality evidence +++**; **Strong recommendation**).
2. Oxytocin should not be started before at least 1 h has elapsed since amniotomy, 6 h since the use of dinoprostone (30 min if vaginal insert) and 4 h since the use of misoprostol (**Low quality evidence +- -**; **Moderate recommendation**).
3. Cardiotocography (CTG) should be performed and a normal pattern without tachysystole should be documented for at least 30 min before oxytocin is used. Continuous CTG, with adequate monitoring of both fetal heart rate and uterine contractions, should be maintained for as long as oxytocin is used, and thereafter until delivery (**Low +- - to moderate +++- quality evidence**; **Strong recommendation**).
4. For labor induction, **at least 1-h should be allowed after amniotomy before oxytocin infusion is started**, to evaluate whether adequate uterine contractility has meanwhile ensued. For augmentation of labor, if the membranes are intact and there are conditions for a safe amniotomy, the latter should be considered before oxytocin is started (**Very low quality evidence +- -**; **Weak recommendation**).
5. Oxytocin should be administered intravenously using the following regimen: 5 IU oxytocin diluted in 500 mL of 0.9% normal saline (NaCl) (each mL contains 10 mIU of oxytocin), in an infusion pump at increasing rates, as shown in [Table 1](#), until a frequency of 3-4 contractions per

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10 min is reached, a non-reassuring CTG pattern ensues, or maximum rates are reached (**Low quality evidence ++ - -; Strong recommendation**). If the frequency of contractions exceeds 5 in 10 min, the infusion rate should be reduced, even if a normal CTG pattern is present. With a non-reassuring CTG pattern, urgent clinical assessment by an obstetrician is indicated, and strong consideration should be given to reducing or stopping the oxytocin infusion. The minimal effective dose of oxytocin should always be used. (**Low ++ - - to Moderate +++ - - quality evidence; Strong recommendation**).

6. Use of oxytocin for induction and augmentation of labor should be regularly audited (**Low quality evidence ++-; Strong recommendation**).

## Introduction

Oxytocin is a neuropeptide produced in the supraoptic and paraventricular nuclei of the hypothalamus. It is a potent uterotonic agent that stimulates the smooth muscle of the uterus and also causes contraction of the myoepithelial cells surrounding the mammary alveoli, leading to milk ejection during lactation [1–6]. The effects of oxytocin are modulated by circulating levels of the hormone, but also by the levels of oxytocinase (an enzyme that degrades oxytocin) and the number and activity of oxytocin receptors. At the onset of labor, there is an upregulation of oxytocin receptor mRNA levels and the density of myometrial oxytocin receptors reaches a peak [7].

Induction of labor is defined as the artificial initiation of uterine contractions before their spontaneous onset, with the purpose of accomplishing vaginal birth. For induction of labor to be successful, cervical ripening, a biomechanical process whereby the cervix becomes soft and compliant, needs to have taken place. The latter may occur naturally or as a result of mechanical or pharmacological interventions, which are outside the scope of this guideline. Augmentation of labor is the process of stimulating the uterus to increase the frequency, duration and intensity of contractions after the onset of labor. It is commonly used to treat protracted or arrested labor, when inadequate uterine contractions are thought to be the underlying cause.

A synthetic analogue of oxytocin is commonly used in clinical practice to induce or augment labor. The solution for injection is colorless and generally available in ampoules containing 5 IU in 1 ml or 10 IU in 1 ml, which must be supplied and stored at temperatures of 2–8 °C. For the purpose of labor induction and augmentation it should only be used by intravenous (IV) infusion. With intravenous use, the half-life of oxytocin is around 3–12 min, depending mostly on its dilution. At an appropriate infusion rate, a gradual response in uterine contractions is elicited within 3–5 min, reaching a steady state within 20–40 min [8,9]. Discontinuation or reduction of the infusion rate leads to a rapid decline in contractile activity. At low

infusion rates it causes rhythmic uterine contractions. In higher doses it has also a direct relaxing effect on vascular smooth muscle, resulting in transient hypotension, reflex tachycardia and flushing.

The uterus is more sensitive to oxytocin as pregnancy advances, as well as in younger women, parous women, women with lower body mass index, women with spontaneous labor onset, and after prostaglandin administration [10–13]. Increased responsiveness also occurs in the late first stage and in the second stage of labor [14]. However, there is a large biological variability in the infusion dose required to cause adequate uterine contractions [2]. For this reason, there is no absolute safe rate, and there is a constant need to titrate the infusion rate against the frequency of uterine contractions [15–18].

In 2007, the Institute for Safe Medication Practices added oxytocin to its list of high-alert medications [19]. Errors involving oxytocin administration are most frequently related to the lack of timely recognition of excessive uterine activity, but also to mistaken administration of IV fluids containing oxytocin, excessive doses leading to transient maternal hypotension, and inappropriate administration. Other risks and side effects associated with the use of oxytocin are: nausea and vomiting; post-partum hemorrhage, especially when a high dose is used during labor, increment intervals are short, or when the patient does not receive prophylactic oxytocin in the third stage of labor; water intoxication with maternal and neonatal hyponatremia (use of high doses of oxytocin together with large amounts of electrolyte-free fluid, related to its anti-diuretic activity); cardiac rhythm disturbances (as a result of interactions with inhalation anesthetics such as cyclopropane, enflurane, halothane and isoflurane) [20–22]. All of these risks are extremely low with the doses used for induction and augmentation of labor, if safe care practices are used.

Induction and augmentation of labor should only be performed when there is a clear medical indication for these procedures, expected benefits outweigh potential harms, and after patient informed consent has been obtained and recorded. Moreover, appropriate staff,

facilities, and equipment need to be present, including professionals with sufficient experience in cardiotocographic (CTG) monitoring and with the capacity to perform an emergency cesarean delivery.

## Recommendations

1. Oxytocin for induction or augmentation of labor **should not be started when there is a previous scar on the body of the uterus** (such as previous classical cesarean section, uterine perforation or myomectomy when uterine cavity is reached) **or in any other condition where labor or vaginal delivery are contraindicated.** (Moderate quality evidence +++-; Strong recommendation).

Uterine rupture secondary to treatment with oxytocin is on average around 2–3 times (ranging from 2 to 14 times) more likely to occur in multiparous women in the context of a previous uterine scar (overall incidence *circa* 1.4–2.1%), when compared with spontaneous labor (overall incidence *circa* 0.15–0.6%), and increases with higher doses of oxytocin [23–25]. Primary uterine rupture is extremely rare (1 in 16,840–1:19,765 in the developed world) [26]. Data regarding primary uterine rupture are limited to a few case-reports and one retrospective case-control study. In this study that compared women with uterine rupture of an unscarred uterus (4.5 in 100,000) with women with uterine rupture of a scarred uterus, a *circa* two-fold increased risk was documented when oxytocin was used in such situations. This is hypothesized to occur mainly when oxytocin perfusion rate is increased despite the occurrence of adequate uterine activity [26]. In the case of a previous scar on the body of the uterus, the evidence is older [27,28], but a 4–9% risk of uterine rupture was described in a meta-analysis[29]; a more recent study that included 157 women who underwent elective cesarean section after a previous classical cesarean section, showed a 9% incidence of dehiscence and one case of spontaneous uterine rupture at 29 weeks ending in perinatal death [30]. Although robust evidence is lacking, when there is a previous scar on the body of the uterus an elective cesarean section is recommended to avoid the risk of rupture and the accompanying maternal and fetal morbidities [31]. Regarding the risk of uterine rupture after myomectomy, the level of evidence is low, mainly based on small case-series. The subsequent risk of uterine rupture probably depends on the type of intervention (number of uterine incisions, type of fibroids removed, laparoscopic or laparotomic approach, etc), but the quality of evidence is low. If the

myomectomy was performed with minimal use of coagulation and uterine closure includes more than one layer, it is probably associated with a low risk of uterine rupture, and a subsequent vaginal delivery may be considered. If the myomectomy involved the whole uterine wall and included entrance in the cavity, this should be considered a contraindication for future vaginal deliveries. Hysteroscopic uterine septum resection or uterine perforation by monopolar coagulation may increase the risk of rupture when compared to an unscarred uterus, but data are insufficient to recommend a planned cesarean section in these cases [23,31]. The decision to induce labor in a pregnant woman with a previous low transverse cesarean section, twins, preterm fetus, fetal growth restriction, as well as a pregnancy with previous cardiovascular disease should be made by a senior obstetrician and recorded in the clinical records.

2. Oxytocin should not be started before at least 1 h has elapsed since amniotomy, 6 h since the use of dinoprostone (30 min if vaginal insert) and 4 h since the use of misoprostol (Low quality evidence +- -; Moderate recommendation).

Minimum time intervals between prostaglandin administration or amniotomy, and the initiation of oxytocin infusion have not been scientifically determined [32]. Therefore the recommendations contained in this guideline are based on the reported half-lives of the different drugs and extrapolations from recommended therapeutic regimens. According to the manufacturer's guidelines: after use of 1.5 mg dinoprostone in intracervical application or 2.5–3.0 mg dinoprostone in vaginal application, oxytocin induction should be delayed for 6–12 h; after use of dinoprostone vaginal insert with sustained-release form, oxytocin use should be delayed for 30–60 min. In addition, oxytocin should not be administered less than 4 h after the last misoprostol dose [32,33]. Oxytocin increases the effect of prostaglandins on uterine contractility and this effect varies according to the formulation used and its pharmacokinetics.

3. Cardiotocography (CTG) should be performed and a normal pattern without tachysystole should be documented for at least 30 min before oxytocin is used. **Continuous CTG, with adequate monitoring of both fetal heart rate and uterine contractions, should be maintained for as long as oxytocin is used, and thereafter until delivery** (Low +- - to moderate +++- quality evidence; Strong recommendation).

The main risk associated with oxytocin infusion is excessive uterine activity, which is usually only

detectable as **tachysystole** (more than **5 contractions in two successive 10 min periods** or **more than 15 contractions in 30 min** [34]). Excessive uterine contractility can result in fetal hypoxia, as the interval between contractions is important for the reestablishment of fetal oxygenation. There are data to suggest that, in spontaneous labor, it takes up to 90 s after a contraction for fetal oxygenation to be restored [35], while in oxytocin-augmented labors this recovery period averages 138 s [34,36,37]. Excessive uterine activity should be avoided, irrespective of whether CTG changes are present or not [18]. This complication can occur at both low and high oxytocin infusion rates.

It is important to document a normal pattern without tachysystole before oxytocin is started, to identify the situations in which its use may be dangerous or unnecessary. Oxytocin should not be started when there is a non-reassuring CTG. Evaluation of the CTG tracing and the decision to start oxytocin is the responsibility of an obstetrician and should be recorded in the clinical records.

4. For labor induction, **at least 1-h should be allowed after amniotomy before oxytocin infusion is started**, to evaluate whether adequate uterine contractility has meanwhile ensued. For augmentation of labor, if the membranes are intact and there are conditions for a safe amniotomy, the latter should be considered before oxytocin is started (**Very low quality evidence +- -; Weak recommendation**).

There is insufficient evidence on the efficacy and safety of amniotomy alone for labor induction [28,38]. Although it can be used for this purpose when the cervix is favorable (modified Bishop score of 6 or above), there is an unpredictable and sometimes long interval before the onset of contractions. Therefore, after amniotomy, 1-h should be allowed before oxytocin infusion is started, to evaluate whether adequate uterine contractility has meanwhile ensued.

Augmentation of labor should not be considered without a clear diagnosis of labor dystocia, as both early amniotomy and routine oxytocin administration during spontaneous labor have not been shown to confer benefits to perinatal outcomes, interventions or birth experiences [39–41]. Before oxytocin infusion is started for labor augmentation, the status of the fetal membranes should be evaluated. If these are intact and there are conditions to carry out an amniotomy safely, consideration should be given to perform this procedure first, as it may be sufficient to provide adequate uterine contractility, and thus avoid the risks of oxytocin infusion. Again, at least 1-h should be

allowed to evaluate the effect of amniotomy on uterine contractility before oxytocin augmentation is considered.

In a systematic review of randomized controlled trials (RCTs) evaluating women with slow progress in the first stage of labor, the use of oxytocin when compared with placebo resulted in a *circa* 2-h reduction in the total duration of labor, an increase in uterine hyperstimulation with CTG changes, and no difference in perinatal outcomes or intervention rates [42]. A systematic review of RCTs comparing the discontinuation versus the continuation of intravenous oxytocin in the active phase of induced labors, reported that the latter results in a *circa* 25-min decreased duration of the active phase of labor and a trend toward decreased chorioamnionitis, but a 85% increase in tachysystole with CTG changes, a 31% increase in cesarean delivery, and no difference in perinatal outcomes [43]. It must be emphasized that abnormal CTG findings and intervention rates may be heavily influenced by oxytocin infusion protocols and by healthcare professionals' reactions to abnormal CTG findings.

5. Oxytocin should be administered intravenously using the following regimen: 5 IU oxytocin diluted in 500 ml of 0.9% normal saline (NaCl) (each mL contains 10 mIU of oxytocin), in an infusion pump at increasing rates, as shown in Table 1, until a frequency of 3–4 contractions per 10 min is reached, a non-reassuring CTG pattern ensues, or maximum rates are reached (**Low quality evidence +- -; Strong recommendation**). If the frequency of contractions exceeds 5 in 10 min, the infusion rate should be reduced, even if a normal CTG pattern is present. With a non-reassuring CTG pattern, urgent clinical assessment by an obstetrician is indicated, and strong consideration should be given to reducing or stopping the oxytocin infusion. The minimal effective dose of oxytocin should always be used. (**Low +- - to Moderate +++ - quality evidence; Strong recommendation**).

Currently there is no generalized agreement on the recommended regimen for oxytocin infusion, and different guidelines propose different regimens [44–57]. Existing evidence does not suggest that any oxytocin regimen is superior to others. In a systematic review of RCTs, comparing high with low dose regimens, no significant differences were found in the rates of vaginal delivery not achieved within 24 h, cesarean delivery, serious maternal morbidity or mortality, or serious neonatal morbidity or perinatal death. No trials reported on the number of women with uterine hyperstimulation with fetal heart rate changes. Removal of studies at high risk of bias revealed that the high-dose group had an almost 2 h reduction in induction to delivery interval and an almost two-fold increase in hyperstimulation (without specifying fetal heart rate changes) [52]. However, there were few

cases of adverse outcomes for mothers and newborns, so the evidence is not strong enough to make firm recommendations.

A major concern is that different oxytocin infusion regimens may be used in the same delivery unit, thus increasing the risk of medication errors. The use of a single oxytocin infusion regimen in the delivery units has been shown to minimize risks [21,57,58]. **In this guideline, a low-dose regimen is proposed, based mainly on safety issues.** When referring to infusion rates of oxytocin, both milliunits/min (mU/min) or milliliters/hour (mL/hour) may be used, but each delivery unit should decide which of these will be used by all staff. The person preparing the oxytocin infusion bag should place an “Oxytocin” drug additive label on it, signing, dating and timing it. The oxytocin starting and increment infusion rates are displayed in Table 1. **Note that when there is a previous uterine scar, the infusion rates are lower.**

The infusion rate should be titrated according to the frequency of uterine contractions, CTG findings and progress of labor. **The minimal effective dose of oxytocin should always be used to obtain 3–4 contractions every 10 min and adequate progress of labor.** Maternal heart rate and the CTG tracing should be evaluated prior to the start or any increase in the infusion rate. Adequate quality of the fetal heart rate and uterine contraction signals needs to be guaranteed. The infusion rate should be reduced if the frequency of contractions exceeds 5 in 10 min, even when a normal CTG pattern is present. With a non-reassuring CTG pattern, urgent clinical assessment by an obstetrician is indicated, and strong consideration should be given to reducing or stopping the oxytocin infusion. External monitoring of uterine contractions

with a tocodynamometer is the technology usually employed in most centers. This only reliably records the frequency of uterine contractions; other characteristics such as duration, intensity, basal tone, and relaxation time between contractions, are also important for fetal oxygenation, but can only be monitored with an intrauterine pressure catheter [34,59]. Excessive uterine contractility can usually be reversed by reducing or stopping the oxytocin infusion, and if a rapid response is required, by starting acute tocolysis with beta-adrenergic agonists (salbutamol, terbutaline, ritodrine), atosiban, or nitroglycerin [34]. If rapid normalization of the CTG pattern does not occur, immediate operative delivery needs to be considered. If oxytocin infusion is discontinued for any reason CTG monitoring should continue until delivery. A decision to recommence oxytocin is the responsibility of a senior obstetrician.

6. Use of oxytocin for labor induction and augmentation should be regularly audited (Low quality evidence +- -; Strong recommendation).

It is the responsibility of healthcare professionals administering oxytocin infusion to record all related clinical findings and procedures appropriately in the patient’s notes, including the timing of increment doses [60]. Regular audit of women undergoing labor induction or augmentation is important to identify communication problems, issues related to guideline implementation, adverse outcomes and intervention rates [60]. This should include an evaluation of severe post-partum hemorrhage, uterine rupture, cesarean delivery, low 5-min Apgar score, newborn metabolic acidosis, and hypoxic-ischemic encephalopathy.

**Table 1.** Recommended oxytocin incremental regimen.


Time	No uterine scar		Previous uterine scar	
	mIU/min	mL/h	mIU/min	mL/h
Start	2	12	1	6
0.5 h	4	24	2	12
1 h	6	36	3	18
1.5 h	8	48	4	24
2 h	10	60	5	30
2.5 h	12	72	6	36
3 h	14	84	7	42
3.5 h	16	96	8	48
		Medical review		
4 h	18	108	9	54
4.5 h	20	120	10	60
5 h	22	132	Maximum dose	
5.5 h	24	144		
6 h	26	156		
6.5 h	28	168		
7 h	30	180		
	Maximum Dose			

## Methodology used in the development of this guideline

The writing group conducted searches in Medline and the Cochrane Library for articles related to this topic. These were limited to studies involving humans and articles published in English between January 1988 and February 2020. The searches were completed manually by consulting the reference list in the identified publications and other guidelines related to the topic. The writing group synthesized the existing evidence, when available, and elaborated the first draft of the manuscript, proposing recommendations according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [61]. Guideline panel members were

asked to comment and modify the text in three successive interactions until a final version of the manuscript was reached. All panel members who agreed with the final version of the document and gave their consent for co-authorship are listed above.

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