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Clinical Expert Summary
Misoprostol (Mysodelle®) 200 microgram vaginal delivery system

Misoprostol (Mysodelle®) for the induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated.

1. Existing guidelines

Clinical experts referred to the National Institute for Health and Care Excellence (NICE) clinical guideline 70 (CG70), Inducing labour (2008), including a surveillance review in 2014 and subsequent report in 2017 that highlighted new evidence and recommended a partial update of the clinical guidelines. Reference was also made to NICE evidence summary 38 (ESNM38): Induction of labour: misoprostol vaginal delivery system.

2. Disease prevalence/incidence

It was estimated that there are approximately 5,000 induced births annually in Wales, but that the contraindications listed for Mysodelle® would exclude a number of women. Clinical experts highlighted that the percentage of women being induced is climbing rapidly and the rate has reached 30% or more in many UK units.

3. Current treatment options

Induction of labour was referred to as a heterogeneous process. The majority of Welsh obstetric units use prostaglandin E2 (also known as dinoprostone) preparations for induction of labour. Dinoprostone is available as a sustained release insert (Propess®) or in tablet or gel form (Prostin E2®). In some units, the use of Propess® is limited to women with unfavourable cervices (low Bishop score).

In women with previous uterine surgery who need induction of labour, some units prefer use of balloon traction catheters to dinoprostone. One expert commented that the Cook cervical ripening balloon, whilst not commonly used, is becoming more popular and is typically used in women who have previously undergone caesarean section. Reference was also made to the use of osmotic cervical dilators in some circumstances.

Following on from cervical ripening (or as an alternative to this in women who have already ruptured their membranes or whose cervices are already dilated), an infusion of oxytocin may be used to stimulate contractions further. Oxytocin is used prior to artificial rupture of membranes in some cases and may also be used alone where there is pre-labour spontaneous rupture of membranes (sometimes with or without prostaglandins depending on urgency of delivery, level of acuity and cervical ripeness). Artificial rupture of membranes may also sometimes be used alone.

Mysodelle® is currently used to induce labour when an intrauterine death has occurred.

4. Unmet needs

The following issues were identified:

- The vaginal agents require repeated vaginal examinations. As well as being uncomfortable and embarrassing for women, repeated vaginal examinations are associated with uterine infection.
- The induction agents usually come in a single dose formulation, although responses to them vary widely between individuals. Thus, a person who is very sensitive will have hyperstimulation of the uterus (population rate about 5%) with an associated risk of fetal hypoxia. Others are very insensitive to the agents and end up with a ‘failed induction’ (rate around 15%) requiring either caesarean section or ‘rest and repeat’. The balance between over-stimulation and under-stimulation is one of the main aspects of successful labour induction.

- The risk of hyperstimulation means that medical labour induction is usually conducted as an inpatient in hospital. This is expensive and tiring for the women who often sleep badly and feel isolated from their families.
- Many of the agents (e.g. dinoprostone tablets or gel) are not removable once inserted. In the event of hyperstimulation, therefore, additional tocolytic drugs are given to suppress the contractions. This is not the case with the vaginal inserts (Propess® or Mysodelle®), which can be removed in the event of uterine hyperstimulation.
- During the pre-labour phase, women receiving dinoprostone often have prolonged periods of 'prostin pains', which require oral analgesia and are exhausting for the woman as they persist for many hours without clinically putting a woman into labour.
- The agents are often expensive.
- Off-label prescribing is common for induction of labour, where the licence excludes most high risk pregnancies.
- The demands on the service are compounded when labour has not ensued or artificial rupture of membranes is not possible within 24 hours, e.g. out-of-hours requests for regional anaesthetic, resulting in further delay in the induction process.
- Mechanical induction using balloon catheters or hydroscopic dilators requires trained medical practitioners.

One clinical expert stated that the current products used are effective in the induction of labour. However, a leading maternity unit in the UK has been using Mysodelle® as the standard inpatient induction agent since December 2017 and it is anticipated that the positive experience reported will result in a number of other units following suit.

5. Knowledge of product in given indication

Although it is more likely that women whose labour is induced will request an epidural, and are therefore at greater risk of instrumental delivery, Mysodelle®, like Propess®, offers solutions to many of the problems outlined in section 4; it is long-acting and inserted only once and so prevents repeat vaginal examinations. Furthermore, it can easily be removed in the event of hyperstimulation as it comes with a removal tab. Mysodelle® appears to have a higher rate of uterine hyperstimulation (13%) than other agents, which may impact maternal and fetal wellbeing and place the unborn fetus at harm. It was suggested that Mysodelle® would be safe, as long as any hyperstimulation is managed, as there was no excess fetal morbidity in the EXPEDITE study. It was suspected that the increase in anxiety regarding the hyperstimulation and fetal heart rate changes will be offset by the efficient onset of effective uterine contractions, leading to no overall difference in satisfaction rates.

A leading maternity unit in the UK has reported a positive experience using Mysodelle® as the standard inpatient induction agent since December 2017. A much quicker response was observed, leading to less maternal exhaustion, less bed occupancy on the labour ward and on the delivery suite, and increased satisfaction all round. It was noted that, as expected, a higher rate of hyperstimulation had been observed in the aforementioned maternity unit, but this was deemed to be easily managed with the removal of the pessary and the occasional use of terbutaline.

One clinical expert stated that Mysodelle® would be used first-line where Prostin E2® is contradicted, where prostaglandin induction is planned, in lower-risk women, and in women with a less favourable cervix (Bishop score < 4). Clinical experts noted that Mysodelle® might not be suitable for outpatient use due to hyperstimulation and rapid onset of action.

The Medicines and Healthcare products Regulatory Agency drug safety update published in February 2018 was noted, highlighting reports of excessive uterine contractions (tachysystole) unresponsive to tocolytic treatment.

It was stated that Mysodelle® is appropriate for specialist-only prescribing.

The higher acquisition cost of Mysodelle® versus Propess® was noted, but it was pointed out there would be other cost implications due to the use of additional tocolytic treatments and the reduced time in labour with Mysodelle® versus Propess®.

It should be noted that one expert involved in compiling this response declared a non-personal specific interest in relation to Mysodelle® for the indication under consideration.