AIMS For a better birth...

Misoprostol for induction of labour: Untested, Unapproved and Unnecessary

Editorial by Beverley Beech

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Doctors here and in the US are using an unlicensed and untested new drug to induce labours. Beverley Beech provides the disturbing background to an ongoing threat to labouring women and their babies.

Synthetic prostaglandins have been used for decades to induce labour or bring about an abortion. Oxytocin, which had been used for a long time to induce labour, caused contractions but did not soften and dilate the cervix - this means strong contractions trying to force a baby out through a still tightly closed cervix.

Prostaglandins both soften the cervix and cause contractions, thereby offering quicker and more "efficient" induction - by obstetric standards. Prostaglandins are naturally occurring hormones, and synthetic prostaglandins are produced by pharmaceutical companies for a variety of medical uses.

Few labouring women know that neither Upjohn Ltd, who produce the prostaglandin gel, or Searle, who produce the misoprostol tablets currently being used for labour induction, have applied for licences for them to be used to induce labour (possibly because they could be sued for damage to mother or child resulting from their use, and settling cases for brain damaged children is very expensive; this means that doctors, or in the UK Trusts bear the burden when things go wrong, not the coffers of the drug company).

When a drug is used for purposes other than which it was intended it is known as an "off-label " drug. Many pharmaceutical companies turn a blind eye to this kind of drug use. After all, they have not had to do expensive research and provide data on safety and adverse effects to licensing authorities and obtain their approval, but they still get the profits from the drugs used for unlicensed purposes.

Doctors can, and often do, use drugs for purposes for which they are not licensed, on their own responsibility. However, we feel that a woman is not giving fully informed consent to their use unless she is told that her prostaglandin induction - whichever product is used - is being done with an unlicensed product for which the drug company takes no responsibility.

The first research on the use of prostaglandins for induction of labour was done in Uganda. At the time AIMS' research officer Jean Robinson expressed concern because we knew how bad women's experiences had been with painful labours induced with oxytocin. She wanted to follow up by contacting

women's groups there to try and get consumer views, but because of the political situation that developed under Idi Amin this became impossible.

International use of prostaglandins escalated, but as with so much other obstetric "progress" there was no qualitative data on women's experiences. We had only the grass roots feedback from mothers about what prostaglandin labours were like and they were becoming even more worrying that the oxytocin story, including cases of ruptured uterus women with caesarean scars.

Recently, consumer attention has focused on misoprostol (Cytotec in the USA), a new prostaglandin that was developed for the treatment of gastric ulcers. Before long doctors discovered that, like other prostaglandins, it was very effective in contracting the uterus and inducing rapid labours. Unlike other prostaglandins, it is cheap - 18p for a 200microgram tablet versus £8.13 for a 3mg prostaglandin tablet. Unlike oxytocin it can be stored at room temperature. It has, therefore, enormous potential for use and misuse in developing countries.

Misoprostol, in common with other prostaglandins, is not licensed for use in labour either in the US, or in the UK, but doctors (and midwives in the US) can use it 'off-label' if they choose to do so - and increasing numbers have. As a result of this, misoprostol was widely used in this way in the US, which has meant that its use in labour is unevaluated and not based on sound medical evidence.

Although some studies have appeared in obstetric journals many are too small to give adequate scientific evidence about the use of this drug in labour, and none of them has sought women's views.

Recently reports begun to emerge of women having ruptured uteri and of babies dying. In 1999 The Cochrane Database of Systematic Reviews published the following statement: 'The increase in uterine hyper-stimulation with fetal heart rate changes is a matter for concern. The studies were not sufficiently large to exclude the possibility of uncommon serious adverse effects. The increase in meconium stained liquor also requires further investigation. Misoprostol (Cytotec) cannot be recommended for routine use for labour induction at this stage. It is also not registered for such use in the US.'

The Warning Letter

In August 2000 Searle issued a warning letter that was sent to 200,000 health care providers in the US (but not to those in the UK) reminding them that 'Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion.' This letter was issued after 'lengthy discussions between Searle and the Federal Drugs Agency after reports were received of uterine rupture in connection with the off-label use of Cytotec in pregnant women.'.

Following this warning the American College of Obstetricians and Gynaecologists (ACOG - the obstetricians' trade union) criticised Searle's statement claiming that misoprostol, when used appropriately, is a safe and effective agent for cervical ripening and labour induction as well as a resource for treating serious postpartum haemorrhage and noted that Searle's letter could limit the availability of misoprostol in women's healthcare.

Yet the Royal College of Obstetricians and Gynaecologists' (RCOG) substantial Evidence-based Clinical Guideline Number 9 - Induction of Labour' devotes a complete chapter to misoprostol and suggests that "There are safety aspects of misoprostol that have not been fully evaluated and it is not currently licensed for obstetric use. Its use must therefore be restricted to RCTs."

In June 2001 the National Institute for Clinical Excellence (NICE) issued their Clinical Guideline on Induction of Labour, but it makes no mention of the RCOG's recommendation that misoprostol should only be used in randomised controlled trials (RCTs), nor is this information contained in their Patients Information Leaflet.

This is a piece of information all women should know. If you are offered a prostaglandin induction your first question should be "Is this part of a randomised trial. If not, why not? Why aren't you following the RCOG recommendation?" Current practices mean that women and babies are exposed to a range of prostaglandins that have never been scientifically evaluated. They are getting the worst of all worlds - being part of an experiment with known serious risks where no one bothers to gather and evaluate the results.

Randomised Controlled Trials

AIMS is in favour of well-designed RCTs to assess the risks and benefits of treatment in obstetrics. We are often, however, concerned about the quality of consent (and not just in RCTs) and, in the case of misoprostol, we are concerned about the validity of any findings a RCT may produce. This is because Searle does not produce this drug in the small quantities required for use in labour, and they have no intention of reducing the size of the tablets in the future.

In order, therefore, to obtain the quantity required the obstetricians have to cut the 200-microgram tablets into two or four pieces. The problem with that is that there is no certainty that the drug is equally distributed through each section. If there is no consistency in the dosage what confidence can one have in any RCT finding?

As far as we can tell RCTs of this drug have taken place in at least four centres in the UK (Aberdeen, Oxford, Liverpool and Ilford) and none of the informed consent leaflets we have obtained to date inform women of the risks of hyper-stimulation. Indeed, an informed consent leaflet from Oxford states that '...this new drug is more effective than prostaglandinE2 gel,with a shorter labour and less need for pain relief, with no increase in side effects on the baby, when administered vaginally.'

More recent work suggests that misoprostol is effective and safe when given orally as well.' This hardly reflected the experience of Jessica Evans who agreed to take part in the Oxford trial (see page 6 for her report).

Informed consent?

A woman who consented to take part in a misoprostol trial in another part of the country informed us that when she was asked to take part in a trial she was told that 'these two drugs (misoprostol and another drug) have been around for a while and we think misoprostol works better, 'if you get it, it will be your lucky day 'cos you will love this drug'.

The woman lost an excessive amount of blood after the birth, had not been told of any risks, and when she commented on the blood loss the midwife said, 'what do you expect you have not had a period for nine months.'

While women are only now beginning to hear about the serious adverse effects of this drug obstetricians are still enthusiastic. At a recent conference an obstetrician said, 'This is a lovely drug it gets the women delivered really quickly.'

When I asked him if he had ever asked the women if they think this is a lovely drug, and who said it was a 'good thing' to have a rapid delivery he made no response. However, current enthusiasm may wane somewhat as the stories of litigation in the US begin to come in. One woman in Oregon, for instance, was awarded £2 million damages following the use of misoprostol. Another in Texas was awarded £1 million damages having suffered a uterine tear caused by the use of the drug.

In a letter to THE LANCET (see page 5) a Birmingham obstetrician suggested that women are losing out by the failure of obstetricians to use this drug in the UK. In June THE LANCET published a critique of that letter by Marsden Wagner (see page 5) who concludes that the huge increase in the use of misoprostol in the US ignores the 28-fold increase in ruptured uteri in women who have had previous caesarean sections and concludes that obstetricians find this drug attractive because of its convenience and the possibility of daylight, Monday to Friday, obstetrics.

In the UK the over-use of induction and acceleration of labour is already a national disgrace. Attention has been focused on the risks of misoprostol because it is not licensed for use in labour but where is the evidence that all the other methods of induction and acceleration are substantially better?

Once a carefully controlled randomised trial is completed and reported there is little or no follow up of the practice that occurs in local hospitals where the standards and criteria required in the trials are not necessarily maintained. Few records are kept of the effects of these drugs on women and babies, unless they are brain damaged or dead.

It is not acceptable for women to be entered into trials that are too small to detect uncommon effects, nor is it acceptable that no questions are asked about the qualitative effect on women and their babies.

Adverse effects of childbirth on women's health are now getting more attention. Yet there have been no independent social science studies of women's experiences. Nor have obstetricians asked questions about long-term effects of prostaglandin inductions on women's mental health, future hormone balance, incidence of premenstrual tension, gynaecological health, incontinence risk or anything else - only the duration of labour, caesarean rate and maybe the average Apgar score of the babies.

In fact, the new misoprostol story is merely the latest chapter in an old story - efficiency of the production line - by obstetric criteria, not ours - with no provision to gather data on short-term, let along long-term effects on the child or the mother.

Over the last forty years there have been massive increases in medicalised births and very little has been done to stem the rise. Are we now to move even further towards daylight obstetrics?