becomes increasingly necessary as gestation progresses and has been recommended for all pregnancies of more than 10 weeks, for pregnancies over 9 weeks in nulliparous women, and for all women younger than 18 years of age.[2,3] It may be achieved by using mechanical dilators, laminaria or synthetic hygroscopic dilators,[1,3] mifepristone, or a prostaglandin such as gemeprost or misoprostol.[1-3] Various drugs, used alone and in combination, have been tried for *medical termination* of pregnancy. Prostaglandins ripen the cervix and stimulate uterine contractility. They can bring about successful termination when used alone, but the high doses required can cause significant adverse effects.[4-6] The most commonly used prostaglandins are gemeprost and misoprostol;[3,4] others that have been used include carboprost and sulprostone, but these have been associated with more severe adverse effects.[3] The antiprogestogen mifepristone also ripens the cervix and stimulates uterine contractility; in addition, it increases the sensitivity of the myometrium to prostaglandins with a maximum effect about 24 to 48 hours after dosing. Mifepristone is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with a prostaglandin, usually gemeprost or misoprostol, to achieve expulsion of the uterine contents.[3-5,7] The antimetabolite methotrexate has also been used with misoprostol, but it has a delayed effect and the time from induction to abortion can be several days or weeks.[4,5] Other methods that have been used for termination of pregnancy, particularly in the second trimester, include intra-amniotic use of dinoprost, hypertonic sodium chloride, or hyperosmolar urea augmented with oxytocin, carboprost, or dinoprost.[1]

Uterine cramping and bleeding are associated with both surgical and medical termination processes. Surgical termination may be carried out under conscious sedation,[1,2] local anaesthesia using paracervical block,[1-3] or general anaesthesia.[2] Analgesia requirements in medical termination may be higher in younger women, nulliparous women, and those with longer gestations.[3,4] Analgesics such as paracetamol, NSAIDs, and codeine are commonly used.[6] Generally, bleeding lasts longer after medical termination than after vacuum aspiration.[6] With medical termination using mifepristone plus a prostaglandin, bleeding is initially heavy but gradually diminishes over about 2 weeks, although minor bleeding can continue for longer.[1,6]

Factors influencing the choice of method for termination include the stage of gestation, availability of surgical services and abortifacient drugs, and the woman's preference. The most common approaches are outlined below.

- In the early first trimester (up to 49 days) a medical method, using mifepristone followed by a prostaglandin, is preferred because the failure rate is higher with vacuum aspiration.[2,6] Methotrexate followed by a prostaglandin is an alternative at this early stage,[1,5] but expulsion can take several days or weeks.[4] Either a surgical or medical method can be used between 49 and 63 days of gestation. However, oral misoprostol for medical termination becomes less effective as gestation progresses[4,5] so a vaginal prostaglandin is preferred.[2,5,6]
- In the late first trimester (up to 13 weeks) a surgical or medical method may be used. After 9 or 10 weeks of gestation, cervical preparation is used before surgical procedures and multiple doses of prostaglandin may be needed to achieve medical termination.[2]
- In mid-trimester termination (13 to 24 weeks) a surgical or medical method may be used. Cervical preparation is essential before surgical termination and multiple doses of prostaglandin will generally be required for medical termination.[2,3]

Some of the methods used for termination of pregnancy are also used to hasten miscarriage after pregnancy failure or early fetal death. Surgical evacuation is effective but associated with a higher risk of infection than expectant management.[8] Vaginal misoprostol can also hasten miscarriage, but oral use is less effective.[9] For the management of intra-uterine fetal death in later pregnancy, see Labour Induction and Augmentation, above.

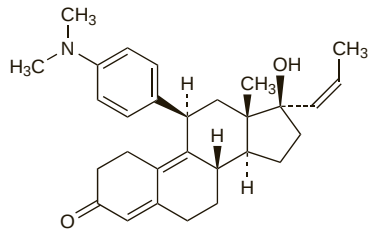
1. Stubblefield PG, *et al.* Methods for induced abortion. *Obstet Gynecol* 2004; **104:** 174–85.
2. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7 (issued September 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/induced_abortionfull.pdf (accessed 30/06/08)
3. Lalitkumar S, *et al.* Mid-trimester induced abortion: a review. *Hum Reprod Update* 2007; **13:** 37–52.
4. Hamoda H, Flett GMM. Medical termination of pregnancy in the early first trimester. *J Fam Plann Reprod Health Care* 2005; **31:** 10–14.
5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, issued October 2005). *Obstet Gynecol* 2005; **106:** 871–82.
6. WHO. Frequently asked clinical questions about medical abortion (2006). Available at: http://www.who.int/reproductive-health/publications/medical_abortion/faq.pdf (accessed 30/06/08)
7. Kulier R, *et al.* Medical methods for first trimester abortion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 30/06/08).
8. Nanda K, *et al.* Expectant care versus surgical treatment for miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
9. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).

Aglepristone *(rINN)*

Aglepristona; Aglépristone; Aglepristonum; RU-46534. 11β-[*p*-(Dimethylamino)phenyl]-17β-hydroxy-17-[(*Z*)-propenyl]estra-4,9-dien-3-one.

Аглепристон

$C_{29}H_{37}NO_2$ = 431.6.
CAS — 124478-60-0.
ATC Vet — QG03XB90.



Profile

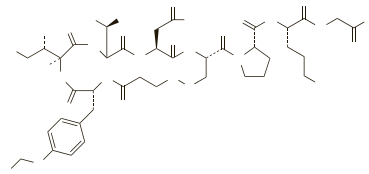
Aglepristone has antiprogestogenic activity and is used in veterinary medicine as an abortifacient in *dogs*.

Atosiban *(BAN, USAN, rINN)*

Atosibaani; Atosibanum; ORF-22164; RWJ-22164. 1-(3-Mercaptopropionic acid)-2-[3-(*p*-ethoxyphenyl)-D-alanine]-4-L-threonine-8-L-ornithineoxytocin; [1-(3-Sulfanylpropanoyl),2-(4-*O*-ethyltyrosine),4-L-threonine-8-L-ornithine]oxytocin.

Атозибан

$C_{43}H_{67}N_{11}O_{12}S_2$ = 994.2.
CAS — 90779-69-4.
ATC — G02CX01.
ATC Vet — QG02CX01.



Adverse Effects and Precautions

Adverse effects reported in women receiving atosiban for premature labour include nausea and vomiting, headache, dizziness, flushes, tachycardia, hypotension, hyperglycaemia, and injection site reactions. Atosiban should not be used where continuation of pregnancy is hazardous to mother or fetus, including where gestational age is below 24 or over 33 weeks, in eclampsia or severe pre-eclampsia, intra-uterine growth retardation and abnormal fetal heart rate, suspected intra-uterine infection, placenta praevia, or abruptio placentae. Monitoring of uterine contractions and fetal heart rate is recommended during use, and blood loss should be monitored after delivery.

Although there has been some concern about fetal exposure, licensed product information states that no specific adverse effects on the newborn have been reported.

Pharmacokinetics

In women in premature labour, atosiban reaches steady-state plasma concentrations within one hour of the start of infusion, and has a terminal half-life of 1.7 hours after stopping infusion. Atosiban is 46 to 48% bound to plasma proteins, and crosses the placenta. It is metabolised to an active metabolite, which is excreted in the urine; both atosiban and this metabolite are distributed into breast milk.

Uses and Administration

Atosiban is a peptide analogue of oxytocin (p.2015) but with oxytocin antagonist properties. It is used as a tocolytic in the management of premature labour (p.2003). Atosiban is given intravenously as the acetate, but doses are expressed in terms of the base. An initial bolus dose equivalent to atosiban 6.75 mg is given by intravenous injection (as a solution containing 7.5 mg/mL) over one minute. This is immediately followed by a continuous infusion of 300 micrograms/minute for 3 hours, then 100 micrograms/minute for up to 45 hours, as a solution containing 750 micrograms/mL. The total duration of treatment should not exceed 48 hours, and the total dose should not exceed 330 mg.

Premature labour. References.

1. Romero R, *et al.* An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000; **182:** 1173–83.
2. Valenzuela GJ, *et al.* Maintenance treatment of preterm labor with the oxytocin antagonist atosiban: the Atosiban PTL-098 Study Group. *Am J Obstet Gynecol* 2000; **182:** 1184–90.
3. Moutquin JM, *et al.* Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. *Am J Obstet Gynecol* 2000; **182:** 1191–9.
4. The Worldwide Atosiban versus Beta-agonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. *Br J Obstet Gynaecol* 2001; **108:** 133–42.
5. The European Atosiban Study Group. The oxytocin antagonist atosiban versus the beta-agonist terbutaline in the treatment of preterm labor: a randomized, double-blind, controlled study. *Acta Obstet Gynecol Scand* 2001; **80:** 413–22.
6. French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. *Eur J Obstet Gynecol Reprod Biol* 2001; **98:** 177–85.
7. Coomarasamy A, *et al.* Oxytocin antagonists for tocolysis in preterm labour—a systematic review. *Med Sci Monit* 2002; **8:** RA268–73.
8. Tsatsaris V, *et al.* Atosiban for preterm labour. *Drugs* 2004; **64:** 375–82.
9. Husslein P, *et al.* Atosiban versus usual care for the management of preterm labor. *J Perinat Med* 2007; **35:** 305–13.

Preparations

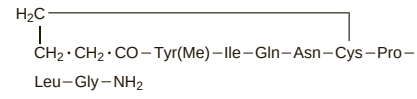
Proprietary Preparations (details are given in Part 3)
Arg.: Tractocile; ***Austria:*** Tractocile; ***Belg.:*** Tractocile; ***Braz.:*** Tractocile†; ***Cz.:*** Tractocile; ***Denm.:*** Tractocile; ***Fin.:*** Tractocile; ***Fr.:*** Tractocile; ***Ger.:*** Tractocile; ***Gr.:*** Tractocile; ***Hong Kong:*** Tractocile; ***Hung.:*** Tractocile; ***Irl.:*** Tractocile; ***Ital.:*** Tractocile; ***Malaysia:*** Tractocile; ***Mex.:*** Tractocile; ***Neth.:*** Tractocile; ***Norw.:*** Tractocile; ***NZ:*** Tractocile; ***Pol.:*** Tractocile; ***Port.:*** Tractocile; ***S.Afr.:*** Tractocile; ***Spain:*** Tractocile; ***Swed.:*** Tractocile; ***Switz.:*** Tractocile; ***UK:*** Tractocile.

Carbetocin *(BAN, rINN)*

Carbetocina; Carbétocine; Carbetocinum; Karbetocin; Karbetosiini. 2,1-Desamino-4,1-desthio-*O*^{4,2}-methyl[1-homocysteine]-oxytocin; 1-Butyric acid-2-[3-(*p*-methoxyphenyl)-L-alanine]oxytocin.

Карбетоцин

$C_{45}H_{69}N_{11}O_{12}S$ = 988.2.
CAS — 37025-55-1.
ATC — H01BB03.
ATC Vet — QH01BB03.



Adverse Effects and Precautions

Carbetocin has similar adverse effects and precautions to those associated with oxytocin when it is used after caesarean section (see p.2015). However, carbetocin should not be used at any stage of labour before delivery of the infant because its effects on the uterus last for several hours.

Breast feeding. In 5 women who were 7 to 14 weeks postpartum, carbetocin was measured in the breast milk within 90 minutes of a single 70-microgram intramuscular dose.[1] The ratio of milk to plasma concentrations was low, suggesting that very little carbetocin was distributed into breast milk. Licensed UK product information states that no significant effects on milk ejection were reported during clinical studies, and that any carbetocin ingested by a breast-fed infant would probably be degraded by enzymes in the gastrointestinal tract. The American Academy of Pediatrics considers that the use of carbetocin is usually compatible with breast feeding.[2]

1. Silcox J, *et al.* Transfer of carbetocin into human breast milk. *Obstet Gynecol* 1993; **82:** 456–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/06/08)