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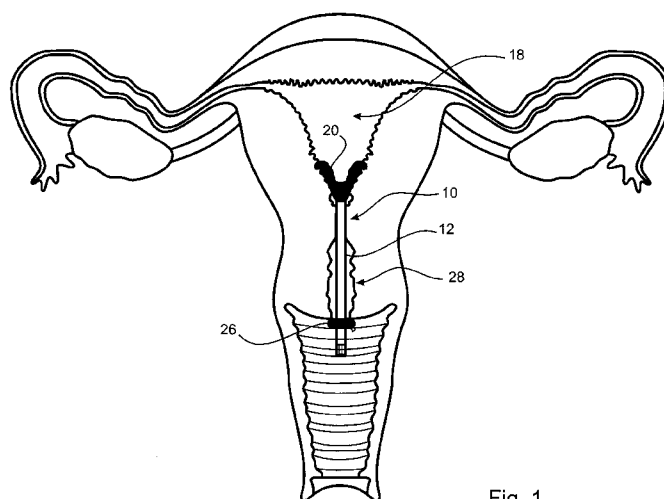


Fig. 1

(57) Abstract: An embryo transfer catheter (10) is described comprising an outer catheter body (12) having first and second lumens (14, 16). The second lumen (16) is adapted to receive an internal catheter (not shown) with a single lumen which, in use, will allow passage of an embryo or embryo-containing cannula (not shown) into the uterus (18) of the recipient. An inflatable balloon (20) is provided at a distal end of the first lumen (14). The inflatable balloon (20) is designed to be as small as possible in its inflated condition whilst still being retained in the uterus (18). The shape of the balloon (20) is adapted in its inflated state to conform to just the lowest part of the uterus (18). The aim in designing the balloon (20) as small as possible is to leave as much endometrium accessible to the embryo for implantation as possible, and to occupy as little volume as possible within the uterine cavity and to exert as little pressure as possible to avoid causing contractions, whilst still being retained in the uterus (18).



“EMBRYO TRANSFER CATHETER AND METHOD”

Field of the Invention

The present invention relates to a new embryo transfer catheter and relates particularly, though not exclusively, to such an embryo transfer catheter for use in an in-vitro fertilisation procedure. The invention also relates to an improved method of transferring embryos in an in-vitro fertilisation procedure.

Background to the Invention

A common assisted reproduction technology, in-vitro fertilisation (IVF) and its derivatives, allows for the retrieval of male sperm & female oocytes by various methods. This is followed by immediate use or storage of these gametes. Fertilisation of the oocyte(s) under strictly controlled conditions occurs immediately or at a later date. Embryos formed by this process are grown in optimal surroundings for a variable time in the laboratory and assessed. The embryos are then replaced in the genital tract, most commonly the uterus, of the female where they will hopefully implant in the endometrium of the uterus, leading to an ongoing pregnancy.

There are many potential points of failure in this overall process. Success rates of IVF have increased slowly but gradually over time. An important step in the IVF process is the replacement of the embryo in the female, most commonly in the uterus. In this step, the clinician examines the female and exposes the uterine cervix with a speculum. The cervix is cleaned. A catheter is inserted through the cervix into the uterine cavity. International Patent Application No PCT/US00/26313 (*Cook Urological Inc*) describes a prior art embryo transfer catheter designed for this purpose. Ultrasound is often used to guide placement. This catheter may be stiff to enable more forceful passage through the cervix, which can be tortuous. Alternatively, the catheter can be soft to allow a passage that follows the anatomy without forcing. Some catheters have both hard and soft sections.

A further internal catheter is inserted through this outer catheter, and its distal end protrudes from the outer catheter as the outer catheter is possibly withdrawn slightly. The inner catheter is then positioned, optimally under ultrasound control, to a point near the fundus, or top, of the uterine cavity.

5 Better results are obtained if this inner catheter is soft and passage is atraumatic. Finally, when correct placement has been judged, a further cannula containing embryos, culture fluid for nourishment, and sometimes air bubbles to aid ultrasound visualisation, is rapidly deployed through the inner catheter, flushed to eject the contents, and then withdrawn with checks to
10 confirm the embryos have been ejected into the uterus. When this is confirmed, all catheters are withdrawn and the patient rests for a variable amount of time. An older technique uses only two catheters, and the inner catheter is used for both positioning and transfer of embryos.

There are several ways that success rates may vary that are attributable to
15 this embryo transfer step in the assisted reproduction process:

1. Passage of the outer catheter though the cervix might be difficult. Manipulation or forceful passage of the catheter leads to irregular contractions in the uterus. When the embryos are inserted, these contractions can lead to the embryos ending in the Fallopian tubes where
20 they may become ectopic pregnancies. Alternatively, contractions may lead to the embryos flushing out through the cervix once the transfer catheter is removed. There is research to show that the number and quality of irregular contractions is correlated with success or failure of embryo transfer. Also, there is research showing reduced success if there
25 is blood and mucus, a sign of traumatic insertion, on the catheter once withdrawn.

2. There may be sub-clinical infection present at the cervix. There is research showing reduced pregnancy success when there is mucopurulent discharge visible at embryo transfer.

30 3. Following removal of the embryo transfer cannula, the embryos may be expelled from the uterus prior to their implantation. This may be the case

even if transfer is easy. Varying periods of bed rest to reduce this chance have been tried with inconclusive results.

4. Even if the embryos remain in the uterus, there may be uterine conditions that prevent or reduce implantation. One reason is the total
5 area of healthy endometrium available for implantation may be reduced by fibroids or a septum in the uterus. Another reason might be that the endometrium has not responded well to hormonal manipulation prior to transfer, and is less receptive. There may be subclinical infection in the cavity or endometrium, perhaps exacerbated by passage of the catheter
10 through an infectious cervix.

Therefore, it could be postulated, embryo quality and other maternal factors being equal, that:

Implantation rate \propto Area and quality of endometrium *

Time in the cavity to allow implantation

15 The present invention was developed with a view to providing a new embryo transfer catheter which may be left securely in situ before and after embryo transfer for several days or longer and which minimises physical disturbance of the endometrium at the time of embryo transfer, and inhibits expulsion of embryos. The invention also provides an improved method of transferring an
20 embryo into the uterine cavity. Although the embryo transfer catheter and method will be described with particular reference to human use, it will be understood that the device and method may also be used with animals.

References to prior art in this specification are provided for illustrative purposes only and are not to be taken as an admission that such prior art is
25 part of the common general knowledge in Australia or elsewhere.

Summary of the Invention

According to one aspect of the present invention there is provided an embryo transfer catheter for transferring an embryo into a uterine cavity of a recipient, the catheter comprising:

an outer catheter body having first and second lumens, the second lumen being adapted to receive an internal catheter which, in use, will allow passage of an embryo-containing cannula or direct passage of an embryo or embryos;

- 5 an inflatable balloon provided at a distal end of the first lumen, the inflatable balloon being designed to be as small as possible in its inflated condition whilst still being retained in the uterus, the shape of the balloon being adapted in its inflated state to conform to just the lowest part of the uterus.

Preferably the balloon is shaped to conform to the lowest part of the uterus
10 both transversely and in an anterior-posterior direction. Preferably the balloon is shaped in a concave way transversely on its superior aspect, which provides the volume necessary for catheter retention and conforms to the transverse uterine shape, but leaves as much endometrium accessible as possible. Preferably the balloon is convex in an anterior-posterior dimension
15 on its superior aspect (to encourage movement of the embryo to the endometrium rather than allow it to rest centrally on the balloon), taking up minimal room in the smaller anterior-posterior dimension of the flattened uterine cavity, whilst still being retained in the uterus.

Typically the balloon comprises first and second arms, which in an inflated
20 state extend upwards transversely within the uterus, at an angle approximating the slope of the inner transverse walls of the flattened uterine cavity.

Another possible variation helps retention of the balloon and hence the catheter. Optionally the balloon may be augmented by inferior protuberances
25 providing extra resistance to expulsion of the catheter. These protuberances typically deflate and become flaccid when the balloon is deflated allowing atraumatic removal. Advantageously these protuberances also enhance the seal of the balloon, when inflated, to the lower part of the uterus, blocking embryo expulsion.

Preferably the portion of the outer catheter body located on the vaginal aspect of the cervix is secured by means of a locking plastic device or an inflatable balloon device for holding the correctly positioned catheter in place more securely following embryo transfer. Either one of these devices
5 preferably slides up and down the outer catheter body prior to being secured or inflated so it lies snugly adjacent to the external aspect of the cervix, securing it in a stable position without movement. This allows for good security, despite variation in the length of the cervix in different women. The locking device or sliding balloon device may have an additional flexible
10 silicone or PVC cover, which envelops the distal end of the catheter, like a bag, preventing colonisation with infective organisms prior to the embryo transfer. This cover is then removed at the time of transfer.

The length of the catheter is such that it limits that portion of its length protruding into the vagina to enhance comfort. However, it still remains
15 accessible in order to allow inflation of the balloon using the first lumen, or passage of catheters through the second lumen. Alternatively, the length of the vaginal portion of the catheter can be longer, even long enough to protrude through the vaginal introitus. This variation would allow easy subsequent embryo transfer without need for another speculum examination.
20 Similarly, removal could then take place without speculum examination.

Advantageously the outer catheter body may be coated with a polymer or membrane, which allows the controlled release of therapeutic substances, locally to the cervix and uterus. Possibly useful therapeutic substances that could be utilised in embryo transfer include:

- 25 • Aspirin (which would inhibit the uterine contractions previously discussed that prevent implantation).
- Antibiotics (to treat prior infection or prevent organisms introduced during transfer causing infection, reducing implantation rates).
- Hormones (to promote growth or receptivity of the endometrium and
30 sustain the pregnancy e.g. oestradiol, oestriol, oestrone and other

- 5 synthetic oestrogenic derivatives, progesterone and other synthetic progestogenic derivatives, growth hormone, growth hormone releasing hormone, DHEA and its isomers, analogues and derivatives, prostacyclin, alpha and beta human chorionic gonadotrophin, luteinising hormone etc.).
- 10 • Corticosteroids, for instance prednisolone, methylprednisolone, hydrocortisone, cortisone, betamethasone, dexamethasone, fluocortolone, triamcinolone, budesonide, their derivatives, analogues, isomers and related class members (to reduce inflammation and promote implantation).
 - 15 • Sildenafil and other phosphodiesterase type 5 inhibitors, their derivatives and their analogues (to enhance endometrial receptivity promoting implantation).
 - Immunomodifiers, for example monoclonal antibodies designed to reduce the activity of inflammatory cells and substances, azathioprine, interferons, immunosuppressants like cyclosporin, tacrolimus, sirolimus and mycophenolate, and endometrial receptor agonists and antagonists.
 - 20 • Calcium channel blockers, for instance Dihydropyridine calcium channel blockers, including but not limited to nifedipine, amlodipine, nicardipine, nimodipine etc; Phenylalkylamine calcium channel blockers like verapamil; Benzothiazepine calcium channel blockers like diltiazem; and non-selective agents like mibefradil, bepridil, fluspirilene, and fendiline (to reduce contractions that diminish successful implantation).
 - 25 • Nitric oxide, nitroglycerine, isosorbide mononitrate, nitroprusside and other nitric acid donors, to reduce contractions and promote implantation.
 - 30 • Growth factors and cytokines (these are under research presently with ill-defined therapeutic effects and clinical indications).

- Local anaesthetics (to reduce any discomfort from the catheter, and also reduce possible signalling within the uterus which may lead to contractions that reduce implantation). Examples are Benzocaine, Chloroprocaine, Cocaine, Cyclomethycaine, Dimethocaine/Larocaine, Piperocaine, Propoxycaine, Procaine/Novocaine, Proparacaine, Tetracaine/Amethocaine, Lidocaine, Articaine, Bupivacaine, Cinchocaine/Dibucaine, Etidocaine, Levobupivacaine, Lidocaine/Lignocaine, Mepivacaine, Prilocaine, Ropivacaine, Trimecaine.
- 5
- 10 According to another aspect of the present invention there is provided an improved method of transferring an embryo into the uterus of a recipient, the method comprising the steps of:
- providing an outer catheter body having first and second lumens, the first lumen having an inflatable balloon provided at its distal end;
- 15 up to several minutes, hours, days or weeks or longer before the actual embryo transfer:
- inserting the outer catheter body into the uterus through the cervix;
- inflating the balloon with fluid so that the outer catheter body is retained in the uterus;
- 20 closing off the second lumen to prevent infection and/or blockage, if embryo transfer is not immediate;
- at the time of the embryo transfer:
- opening the second lumen in the outer catheter body;
- inserting a matching internal catheter into the second lumen;
- 25 passing an embryo-containing cannula through the internal catheter to transfer an embryo into the uterus;

or, alternatively, passing only one catheter, already containing embryos, through the second lumen and transferring the embryos directly;

following embryo transfer:

reclosing the second lumen; and,

- 5 retaining the outer catheter body in the uterus for up to several hours or days after the embryo transfer wherein, in use, the transferred embryo or embryos are prevented from expulsion by obstruction of the cervix and physical disturbance of the endometrium can be minimised.

Possibly the balloon may be temporarily partially deflated during the embryo
10 transfer to allow adjacent passage of the internal soft catheter into the uterine cavity. If so, the balloon is reinflated immediately after embryo transfer and removal of the embryo-bearing cannula or catheter.

Typically the step of closing off the second lumen in the outer catheter body is performed by inserting a removable flexible plastic stent that is lockable in
15 position by a locking mechanism. The locking mechanism may be a Luer-Lok (Trademark). Preferably the step of opening the second lumen is performed by removing the flexible stent. Typically the step of reclosing the second lumen is performed by inserting a new flexible stent in the second lumen to occlude it. Alternatively, the second lumen is closed by means of a self-
20 closing lid at the distal aspect and a lid or cap at the proximal end.

Advantageously step of inserting the embryo transfer catheter through the cervix and into the uterine cavity includes placing a tight-fitting covering or sleeve received over the catheter to protect the catheter from contacting any cervical mucus or infection. Once the catheter has been inserted into the
25 uterus, the sleeve is preferably removed by simply pulling it distally. Preferably the sleeve is split at the top allowing its removal so as to leave the catheter in place.

Advantageously the method further comprises the step of controlled release of therapeutic substances via the outer catheter, locally to the cervix and uterus.

Throughout the specification, unless the context requires otherwise, the word
5 “comprise” or variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Likewise the word “preferably” or variations such as “preferred”, will be understood to imply that
10 a stated integer or group of integers is desirable but not essential to the working of the invention.

Brief Description of the Drawings

The nature of the invention will be better understood from the following detailed description of several specific embodiments of an embryo transfer
15 catheter and improved method of embryo transfer, given by way of example only, with reference to the accompanying drawings, in which:

Figure 1 illustrates a first embodiment of an embryo transfer catheter inserted into a uterus through the cervix of the recipient;

20 Figure 2 illustrates the shape of a balloon on the distal end of the embryo transfer catheter of Figure 1 in its inflated state;

Figure 3 is a cross-section view of the outer catheter body of the embryo transfer catheter of Figure 1;

Figure 4 illustrates a sleeve for insertion of the embryo transfer catheter of Figure 1;

25 Figure 5 is a top plan view of the embryo transfer catheter of Figure 1 with the balloon in a semi-inflated state; and,

Figure 6 is a cross-section view of an alternative design for the outer catheter body of the embryo transfer catheter.

Detailed Description of Preferred Embodiments

A first embodiment of an embryo transfer catheter 10 in accordance with the invention, as illustrated in Figures 1 to 3, comprises an outer catheter body 12 having first and second lumens 14, 16 (see Figure 3), the second lumen 5 16 being adapted to receive an internal catheter (not shown) with a single lumen which, in use, will allow passage of an embryo or embryo-containing cannula (not shown) into the uterus 18 of the recipient. An inflatable balloon 20 is provided at a distal end of the first lumen 14. The inflatable balloon 20 is designed to be as small as possible in its inflated condition whilst still being 10 retained in the uterus 18. The shape of the balloon 20 is adapted in its inflated state to conform to just the lowest part of the uterus 18.

The aim in designing the balloon 20 as small as possible is to leave as much endometrium accessible to the embryo for implantation as possible, and to occupy as little volume as possible within the uterine cavity and to exert as 15 little pressure as possible to avoid causing contractions, whilst still being retained in the uterus 18. Figure 5 shows the profile of the balloon 20 when viewed in top plan view, in a semi-inflated state. In Figure 5 the second lumen 16 is occluded by a stent 30 (or alternatively a lid).

Preferably the balloon 20 is shaped to conform to the lowest part of the 20 uterus 18 both transversely and in an anterior-posterior direction. Preferably the balloon is shaped in a concave way transversely on its superior aspect, which provides the volume necessary for catheter retention and conforms to the transverse uterine shape, but leaves as much endometrium accessible as possible. Preferably the balloon is convex in an anterior-posterior dimension 25 on its superior aspect (to encourage movement of the embryo to the endometrium rather than allow it to rest centrally on the balloon), taking up minimal room in the smaller anterior-posterior dimension of the flattened uterine cavity, whilst still being retained.

In the illustrated embodiment the balloon 20 comprises first and second arms 30 22, which in an inflated state extend upwards transversely within the uterus

18, at an angle approximating the slope of the inner transverse walls of the flattened uterine cavity.

Other possible variations help retention of the balloon 20 and hence the catheter: Optionally the balloon 20 may be augmented by inferior
5 protuberances 24 providing extra resistance to expulsion of the catheter body 12. Several protuberances may be provided on each balloon to enhance tactile resistance to expulsion. These protuberances 24 typically deflate and become flaccid when the balloon 20 is deflated allowing atraumatic removal. Advantageously these protuberances 24 also enhance the seal of the balloon
10 20 to the lower part of the uterus 18, blocking embryo expulsion.

The use of protuberances on the balloon 20 is not the only way to secure the catheter within the uterus. For example, an assembly of two similarly shaped plastic arms with distal hinges could be deployed. The plastic arms would be straight (continuous with the catheter) upon insertion, but could then be
15 pushed transversely, articulating via their hinges, at a chosen time by using the stent, pressing on a plastic protuberance. Then when removal occurs, the stent can be pulled out, allowing the plastic arms to fold back vertically facilitating catheter extraction.

Preferably the portion of the outer catheter body 12 on the vaginal aspect of
20 the cervix is secured by means of a plastic locking device or an inflatable locking balloon device 26 for holding the correctly positioned catheter in place more securely following embryo transfer. Either one of these devices preferably slides up and down the outer catheter body 12 prior to being secured or inflated, so that it lies snugly adjacent to the external aspect of the
25 cervix 28, securing it in a stable position without movement, as shown in Figure 1. This allows for secure retention of the catheter 10, despite variation in the length of the cervix in different women. The locking device or sliding balloon device may have an additional flexible silicone or PVC cover, which envelops the distal end of the catheter, like a bag, preventing colonisation
30 with infective organisms prior to the embryo transfer. This cover is then removed at the time of transfer. The portion of the outer catheter body 12 on

the vaginal aspect of the cervix can also be secured by simply using an increased friction technique. Current devices all use this simple friction technique.

The length of the catheter 10 is such that it limits that portion of its length protruding into the vagina to enhance comfort. However, it still remains accessible in order to allow inflation of the balloon 20 using the first lumen 14, or passage of catheters through the second lumen 16. Alternatively, the length of the vaginal portion of the catheter can be longer, even long enough to protrude through the vaginal introitus. This variation would allow easy subsequent embryo transfer without need for another speculum examination. Similarly, removal could then take place without speculum examination. This extra length would be advantageous when the catheter is only planned to be left for up to a few hours after embryo transfer.

A removable flexible plastic stent 30, that is lockable by a locking mechanism, typically a Luer-Lok (Trademark) or similar, is provided to close off the second lumen 16 prior to embryo insertion, to prevent infection and/or blockage. The top of the stent 30 would typically be gently convex to match the adjacent parts of the balloon 20. This stent 30 is removed for the embryo transfer, and subsequently replaced with a matching internal catheter with a single lumen, which then allows passage of the embryo or embryo-containing cannula.

In Figure 3 it can be seen how the cross-sectional shape of the first lumen 14 (for balloon inflation) of the outer catheter body 12 is crescent shaped. Figure 6 illustrates an alternative cross-sectional design for the outer catheter body, in which the first lumen 14 is of circular shape.

Advantageously the outer catheter body 12 may be coated with a polymer or membrane, which allows the controlled release of therapeutic substances, locally to the cervix 28 and uterus 18. Possibly useful therapeutic substances that could be utilised in embryo transfer include:

- Aspirin (which would inhibit the uterine contractions previously discussed that prevent implantation).
- Antibiotics (to treat prior infection or prevent organisms introduced during transfer causing infection, reducing implantation rates).
- 5 • Hormones (to promote growth or receptivity of the endometrium and sustain the pregnancy eg. oestradiol, oestriol, oestrone and other synthetic oestrogenic derivatives, progesterone and other synthetic progestin derivatives, growth hormone, growth hormone releasing hormone, DHEA and it's isomers, analogues and derivatives,
10 prostacyclin, alpha and beta human chorionic gonadotrophin, luteinising hormone etc.)
- Corticosteroids, for instance prednisolone, methylprednisolone, hydrocortisone, cortisone, betamethasone, dexamethasone, fluocortolone, triamcinolone, budesonide, their derivatives, analogues,
15 isomers and related class members (to reduce inflammation and promote implantation).
- Sildenafil and other phosphodiesterase type 5 inhibitors, their derivatives and their analogues (to enhance endometrial receptivity promoting implantation).
- 20 • Immunomodifiers, for example monoclonal antibodies designed to reduce the activity of inflammatory cells and substances, azathioprine, interferons, immunosuppressants like cyclosporin, tacrolimus, sirolimus and mycophenolate, and endometrial receptor agonists and antagonists.
- 25 • Calcium channel blockers, for instance Dihydropyridine calcium channel blockers, including but not limited to nifedipine, amlodipine, nicardipine, nimodipine etc; Phenylalkylamine calcium channel blockers like verapamil; Benzothiazepine calcium channel blockers like diltiazem; and non-selective agents like mibefradil, bepidil,

fluspirilene, and fendiline (to reduce contractions that diminish successful implantation).

- Nitric oxide, nitroglycerine, isosorbide mononitrate, nitroprusside and other nitric acid donors, to reduce contractions and promote
5 implantation.
- Growth factors and cytokines (these are under research presently with ill-defined therapeutic effects and clinical indications).
- Local anaesthetics (to reduce any discomfort from the catheter, and also reduce possible signalling within the uterus which may lead to
10 contractions that reduce implantation). Examples are Benzocaine, Chloroprocaine, Cocaine, Cyclomethycaine, Dimethocaine/Larocaine, Piperocaine, Propoxycaine, Procaine/Novocaine, Proparacaine, Tetracaine/Amethocaine, Lidocaine, Articaine, Bupivacaine, Cinchocaine/Dibucaine, Etidocaine, Levobupivacaine,
15 Lidocaine/Lignocaine, Mepivacaine, Prilocaine, Ropivacaine, Trimecaine.

Advantageously the embryo transfer catheter 10 may be inserted through the cervix and into the uterine cavity within a tight-fitting covering or sleeve 40 (made of silicone or PVC or other non-embryo toxic flexible material),
20 illustrated in Figure 4. The sleeve 40 has a split at the top with overlapping portions. Once the catheter 10 has been inserted into the uterus, this silicone sleeve 40 is removed by simply pulling it distally, the split at the top allowing its removal leaving the catheter 10 in place. The sleeve 40 protects the catheter 10 from contacting any cervical mucus or infection. The sleeve 40
25 may be slightly textured or absorbent. This texture or absorbency encourages adherence of any cervical mucus brought into the uterus during the insertion, and thus allows the removal of this mucus when the sleeve 40 is removed.

A preferred method of transferring an embryo into the uterus 18 of a recipient
30 will now be described with reference to Figure 1. The method firstly

comprises the step of providing an outer catheter body 12 having first and second lumens 14, 16, the first lumen having an inflatable balloon 20 provided at its distal end, as described above. The outer catheter body 12 may be inserted into the uterus 18 through the cervix 28 several hours or preferably several days or weeks or longer before the actual embryo transfer, instead of immediately prior as in current practice. Then the balloon 20 is inflated with fluid (liquid or gas) so that the outer catheter body 12 is retained in the uterus and cervix 18. The removable flexible plastic stent 30 is already placed to close off the second lumen 16 to prevent infection and/or blockage. Alternatively, the second lumen is closed by means of a lid at the distal aspect, and a lid or cap at the proximal end.

At the time of the embryo transfer the stent 30 is removed to open the second lumen in the outer catheter body for the embryo transfer. This stent is replaced with a matching internal catheter (not shown) with a single lumen, which then allows passage of the embryo, or alternatively an embryo-containing cannula to transfer an embryo into the uterus 18. The balloon 20 may be temporarily partially deflated during the embryo transfer to allow adjacent passage of the internal soft catheter into the uterine cavity. If so, it is reinflated immediately after embryo transfer and removal of the embryo-bearing cannula or catheter.

A new flexible stent 30 is placed in the second lumen 16 to occlude it following embryo transfer to reclose the second lumen 16. Alternatively, the distal lid closes following removal of the passed catheter and a cap or lid occludes the lumen on its proximal aspect. The outer catheter body 12 may be retained in the uterus 18 for up to several minutes, hours or days after the embryo transfer wherein, in use, physical disturbance of the endometrium can be minimised. The catheter's design allows it to be left securely in situ after embryo transfer for several days, which potentially increases success rates, by several methods, most importantly, by blockage of the exit of the uterus preventing expulsion of the embryo, and by further local delivery of therapeutic substances from the catheter body.

The possible advantages of prior insertion are:

- it allows for uterine contractions to settle if insertion is difficult
- it reduces the stress surrounding the embryo transfer
- it allows for timely insertion under anaesthetic if insertion failure occurs
- 5 • it allows local delivery of therapeutic substances over a period of time prior to embryo transfer (as described below).

Now that preferred embodiments of the embryo transfer catheter and method
10 of embryo transfer have been described in detail, it will be apparent that the described embodiments provide a number of advantages over the prior art, including the following:

- (i) Retention of the embryo transfer catheter pre-insertion allows for uterine contractions to settle if insertion is difficult.
- 15 (ii) It reduces the stress surrounding the embryo transfer.
- (iii) It allows for timely insertion under anaesthetic if insertion failure occurs.
- (iv) It allows local delivery of therapeutic substances over a period of time prior to embryo transfer.
- 20 (v) Retention of the embryo transfer catheter post-insertion ensures blockage of the exit of the uterus preventing expulsion of the embryo.
- (vi) It maximizes contact of the embryo with the endometrium.
- (vii) It also allows the local delivery of therapeutic substances over a period
of time after embryo transfer which could enhance pregnancy rates by
25 virtue of decreasing uterine contractions, reducing infection, immune response & inflammation, and delivery of hormones or growth factors.

It will be readily apparent to persons skilled in the relevant arts that various
modifications and improvements may be made to the foregoing
30 embodiments, in addition to those already described, without departing from the basic inventive concepts of the present invention. For example, the

shape of the balloon at the distal end of the outer catheter body may vary significantly from that shown in the illustrated embodiments. The balloon may be of any suitable shape that leaves as much endometrium accessible to the embryo for implantation as possible, occupies as little volume as possible
5 within the uterine cavity and exerts as little pressure as possible to avoid causing contractions, whilst still being retained in the uterus. Therefore, it will be appreciated that the scope of the invention is not limited to the specific embodiments described, and is to be determined from the appended claims.

Claims

1. An embryo transfer catheter for transferring an embryo into a uterine
5 cavity of a recipient, the catheter comprising:

an outer catheter body having first and second lumens, the second lumen
being adapted to receive an internal catheter which, in use, will allow
passage of an embryo-containing cannula or direct passage of an embryo
or embryos;
- 10 an inflatable balloon provided at a distal end of the first lumen, the inflatable
balloon being designed to be as small as possible in its inflated condition
whilst still being retained in the uterus, the shape of the balloon being
adapted in its inflated state to conform to just the lowest part of the uterus.
2. An embryo transfer catheter as defined in claim 1, wherein the balloon is
15 shaped to conform to the lowest part of the uterus both transversely and in
an anterior-posterior direction.
3. An embryo transfer catheter as defined in claim 2, wherein the balloon is
shaped in a concave way transversely on its superior aspect, which
provides the volume necessary for catheter retention and conforms to the
20 transverse uterine shape, but leaves as much endometrium accessible as
possible.
4. An embryo transfer catheter as defined in claim 3, wherein the balloon is
convex in an anterior-posterior dimension on its superior aspect (to
encourage movement of the embryo to the endometrium rather than allow it
25 to rest centrally on the balloon), taking up minimal room in the smaller
anterior-posterior dimension of the flattened uterine cavity, whilst still being
retained in the uterus.
5. An embryo transfer catheter as defined in any one of claims 1 to 4,
wherein the balloon comprises first and second arms, which in an inflated
30 state extend upwards transversely within the uterus, at an angle

approximating the slope of the inner transverse walls of the flattened uterine cavity.

6. An embryo transfer catheter as defined in any one of the preceding claims, wherein the balloon is augmented by inferior protuberances helping
5 retention of the balloon and providing extra resistance to expulsion of the catheter.

7. An embryo transfer catheter as defined in claim 6, wherein the protuberances deflate and become flaccid when the balloon is deflated allowing atraumatic removal.

10 8. An embryo transfer catheter as defined in claim 6, wherein the protuberances also enhance the seal of the balloon, when inflated, to the lower part of the uterus, blocking embryo expulsion.

9. An embryo transfer catheter as defined in claim 1, wherein a portion of the outer catheter body located on the vaginal aspect of the cervix is
15 secured by means of a locking plastic device or an inflatable balloon device for holding the correctly positioned catheter in place more securely following embryo transfer.

10. An embryo transfer catheter as defined in claim 9, wherein either one of the devices slides up and down the outer catheter body prior to being
20 secured or inflated so it lies snugly adjacent to the external aspect of the cervix, securing it in a stable position without movement.

11. An embryo transfer catheter as defined in claim 9, wherein the locking device or sliding balloon device has an additional flexible silicone or PVC cover, which envelops the distal end of the catheter, like a bag, preventing
25 colonisation with infective organisms prior to the embryo transfer.

12. An embryo transfer catheter as defined in any one of the preceding claims, wherein the length of the catheter is such that it limits that portion of its length protruding into the vagina to enhance comfort, but still remains

accessible in order to allow inflation of the balloon using the first lumen, or passage of catheters through the second lumen.

13. An embryo transfer catheter as defined in any one of the preceding claims, wherein the length of the vaginal portion of the catheter is longer,
5 even long enough to protrude through the vaginal introitus, to allow easy subsequent embryo transfer without need for another speculum examination.

14. An embryo transfer catheter as defined in any one of the preceding claims, wherein the outer catheter body is coated with a polymer or
10 membrane, which allows the controlled release of therapeutic substances, locally to the cervix and uterus.

15. An embryo transfer catheter as defined in claim 14, wherein possibly useful therapeutic substances that could be utilised in embryo transfer include:

- 15 • Aspirin (which would inhibit the uterine contractions previously discussed that prevent implantation).
- Antibiotics (to treat prior infection or prevent organisms introduced during transfer causing infection, reducing implantation rates).
- 20 • Hormones (to promote growth or receptivity of the endometrium and sustain the pregnancy e.g. oestradiol, oestriol, oestrone and other synthetic oestrogenic derivatives, progesterone and other synthetic progestogenic derivatives, growth hormone, growth hormone releasing hormone, DHEA and its isomers, analogues and derivatives, prostacyclin, alpha and beta human chorionic
25 gonadotrophin, luteinising hormone etc.).
- Corticosteroids, for instance prednisolone, methylprednisolone, hydrocortisone, cortisone, betamethasone, dexamethasone, fluocortolone, triamcinolone, budesonide, their derivatives, analogues, isomers and related class members (to reduce

inflammation and promote implantation).

- Sildenafil and other phosphodiesterase type 5 inhibitors, their derivatives and their analogues (to enhance endometrial receptivity promoting implantation).
- 5
- Immunomodifiers, for example monoclonal antibodies designed to reduce the activity of inflammatory cells and substances, azathioprine, interferons, immunosuppressants like cyclosporin, tacrolimus, sirolimus and mycophenolate, and endometrial receptor agonists and antagonists.
- 10
- Calcium channel blockers, for instance Dihydropyridine calcium channel blockers, including but not limited to nifedipine, amlodipine, nicardipine, nimodipine etc; Phenylalkylamine calcium channel blockers like verapamil; Benzothiazepine calcium channel blockers like diltiazem; and non-selective agents like mibefradil, bepidil, fluspirilene, and fendiline (to reduce contractions that diminish successful implantation).
- 15
- Nitric oxide, nitroglycerine, isosorbide mononitrate, nitroprusside and other nitric acid donors, to reduce contractions and promote implantation.
- 20
- Growth factors and cytokines (these are under research presently with ill-defined therapeutic effects and clinical indications).
 - Local anaesthetics (to reduce any discomfort from the catheter, and also reduce possible signalling within the uterus which may lead to contractions that reduce implantation). Examples are Benzocaine, Chloroprocaine, Cocaine, Cyclomethycaine, Dimethocaine/Larocaine, Piperocaine, Propoxycaine, Procaine/Novocaine, Proparacaine, Tetracaine/Amethocaine, Lidocaine, Articaine, Bupivacaine, Cinchocaine/Dibucaine, Etidocaine, Levobupivacaine, Lidocaine/Lignocaine, Mepivacaine, Prilocaine, Ropivacaine, Trimecaine.
- 25
- 30

16. An improved method of transferring an embryo into the uterus of a recipient, the method comprising the steps of:

providing an outer catheter body having first and second lumens, the first lumen having an inflatable balloon provided at its distal end;

5 up to several minutes, hours, days or weeks or longer before the actual embryo transfer:

inserting the outer catheter body into the uterus through the cervix;

inflating the balloon with fluid so that the outer catheter body is retained in the uterus;

10 closing off the second lumen to prevent infection and/or blockage;

at the time of the embryo transfer:

opening the second lumen in the outer catheter body;

inserting a matching internal catheter into the second lumen;

15 passing an embryo or embryo-containing cannula through the internal catheter to transfer an embryo into the uterus;

following embryo transfer:

reclosing the second lumen; and,

20 retaining the outer catheter body in the uterus for up to several hours or days or longer after the embryo transfer wherein, in use, the transferred embryo or embryos are prevented from expulsion by obstruction of the cervix and physical disturbance of the endometrium can be minimised.

17. An improved method of transferring an embryo as defined in claim 16, wherein the balloon may be temporarily partially deflated during the embryo transfer to allow adjacent passage of the internal soft catheter into the
25 uterine cavity.

18. An improved method of transferring an embryo as defined in claim 17, wherein the balloon is reinflated immediately after embryo transfer and removal of the embryo-bearing cannula or catheter.
19. An improved method of transferring an embryo as defined in claim 16,
5 wherein the step of closing off the second lumen in the outer catheter body is performed by inserting a removable flexible plastic stent that is lockable in position by a locking mechanism.
20. An improved method of transferring an embryo as defined in claim 19,
10 wherein the step of opening the second lumen is performed by removing the flexible stent.
21. An improved method of transferring an embryo as defined in claim 20, wherein the step of reclosing the second lumen is performed by inserting a new flexible stent in the second lumen to occlude it.
22. An improved method of transferring an embryo as defined in claim 20,
15 wherein the second lumen is reclosed by means of a self-closing lid at the distal aspect and a lid or cap at the proximal end.
23. An improved method of transferring an embryo as defined in any one of claims 16 to 22, wherein the step of inserting the embryo transfer catheter through the cervix and into the uterine cavity includes placing a tight-fitting
20 covering or sleeve received over the catheter to protect the catheter from contacting any cervical mucus or infection.
24. An improved method of transferring an embryo as defined in claim 23, wherein once the catheter has been inserted into the uterus, the sleeve is preferably removed by simply pulling it distally.
25. An improved method of transferring an embryo as defined in any one of
25 claims 16 to 24, wherein the method further comprises the step of controlled release of therapeutic substances via the outer catheter, locally to the cervix and uterus.

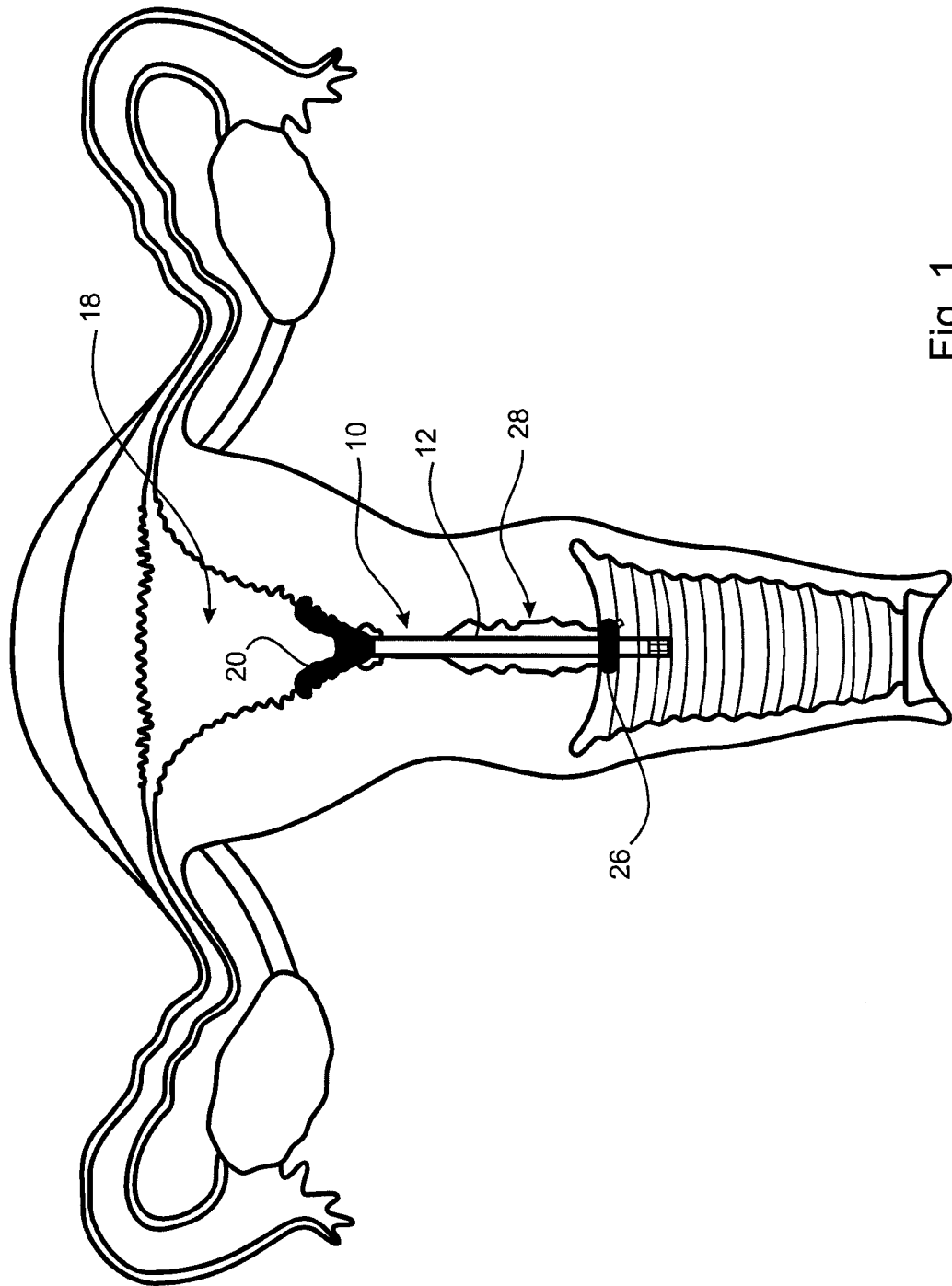


Fig. 1

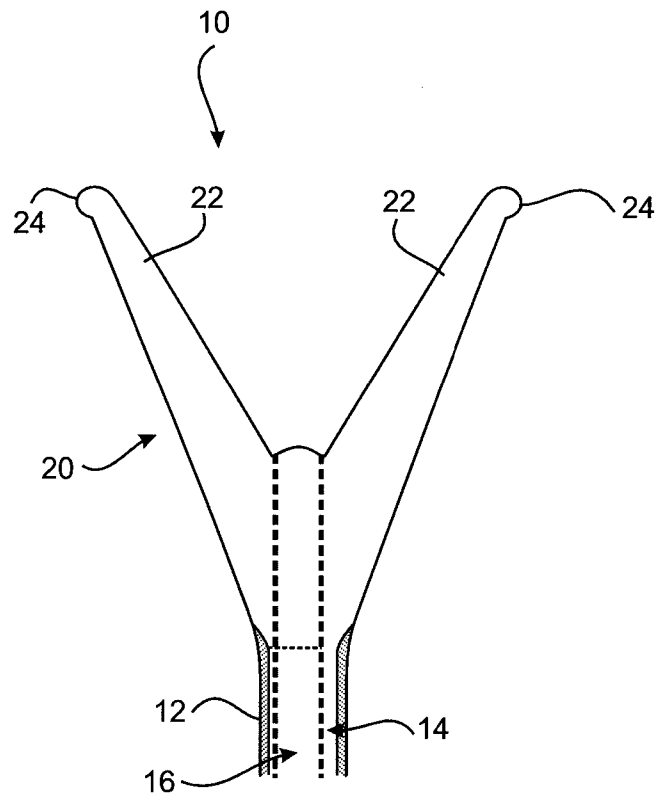


Fig. 2

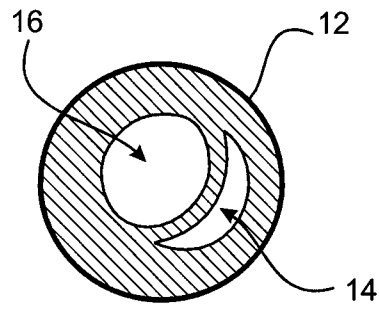


Fig. 3

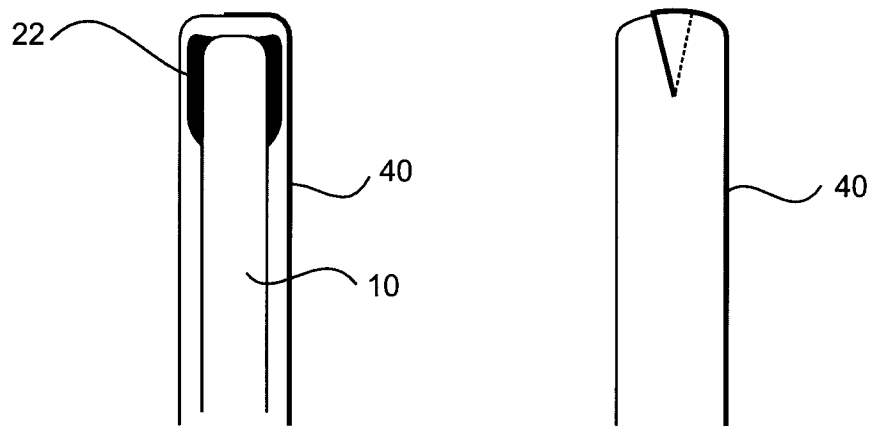


Fig. 4

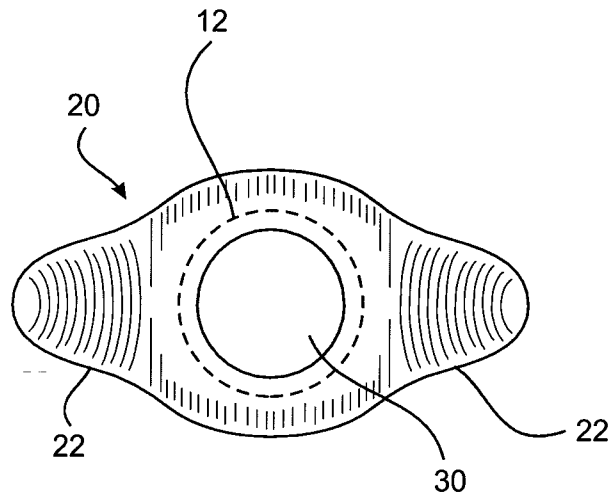


Fig. 5

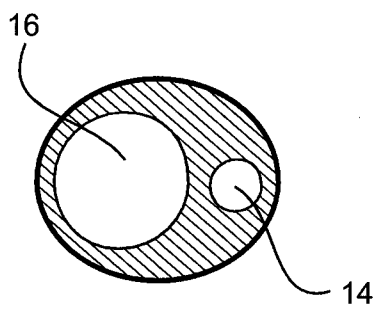


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2014/000091

A. CLASSIFICATION OF SUBJECT MATTER

A61B 17/435 (2006.01) A61M 25/10 (2013.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC: cervix, uterus, balloon, cuff, drug, slow, continuous, sustained, womb, embryo and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

 Further documents are listed in the continuation of Box C
 See patent family annex

* Special categories of cited documents:		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 March 2014	Date of mailing of the international search report 13 March 2014
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaaustralia.gov.au Facsimile No.: +61 2 6283 7999	Authorised officer Dr. Steven Weiss AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832352

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).		PCT/AU2014/000091
DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 5904665 A (MUHARIB) 18 May 1999 column 2 lines 41-63, column 3 lines 18-27 column 2 lines 41-63, column 3 lines 18-27	1-3, 13 14
X Y	US 2006/0058831 A1 (ATAD) 16 March 2006 items 59, 62, 66, 69 and 70, figures 3D to 3G, 4D and 4E, and paragraphs [0021], [0022], [0023], [0104], [0107], [0110]-[0112], [0140], [0141], and [0186] items 59, 62, 66, 69 and 70, figures 3D to 3G, 4D and 4E, and paragraphs [0021], [0022], [0023], [0104], [0107], [0110]-[0112], [0140], [0141], and [0186]	1-4, 6, 9, 13 14
Y	WO 2012/013229 A1 (FONDAZIONE IRCCS) 02 February 2012 figures 2 and 4, and page 18 line 8 - page 19 line 9	14
A	COOK MEDICAL. 2009 Product Catalog - Assisted Reproductive Technology. [retrieved from internet on 12 March 2014] URL: http://www.medial.cz/data/files/medial/download/katalogy/Cook/Cook_ivf_katalog.pdf Published in 2009 as per title Sydney IVF Embryo Transfer Catheter Sets page 62	1-4, 6, 9, 13
A	Medical Device KITAZATO ET CATHETERS 3FR 22CM - 213322 [retrieved from internet on 12 March 2014] URL: http://www.medicaldevices24.com/medical_devices/info/kitazato-et-catheters-3fr-22cm/412702 published on 28 September 2012 (as stated in table) 3Fr disclosed in title	1-4, 6, 9, 13
A	US 5562654 A (SMITH) 08 October 1996 Figure 2	

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/AU2014/000091	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 5904665 A	18 May 1999	None	
US 2006/0058831 A1	16 Mar 2006	None	
WO 2012/013229 A1	02 Feb 2012	EP 2598114 A1	05 Jun 2013
		US 2013211384 A1	15 Aug 2013
		WO 2012013229 A1	02 Feb 2012
US 5562654 A	08 Oct 1996	None	
End of Annex			
<p>Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)</p>			