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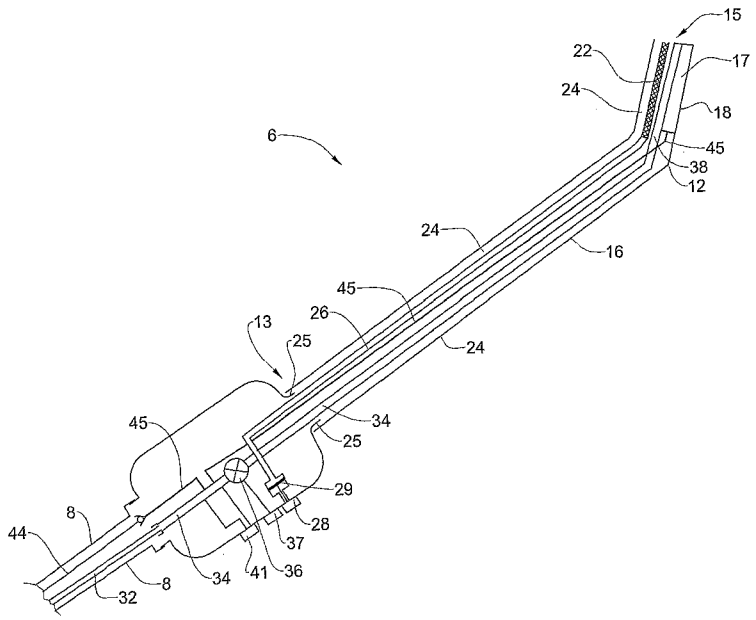
(54) Title: SYSTEM AND METHOD FOR TRANSFETAL (AMNION-CHORION) MEMBRANES TRANSPORT



(57) Abstract: The invention provides a system and method for trans-fetal membranes transport. A source of ultrasound sonication is used to deliver ultrasound sonication to fetal membranes to enhance the permeability of the fetal membranes of a gestational sac. In one embodiment, a device is used to collect substances transported from the interior of the gestational sac to the exterior of the gestational sac, such as amniotic or coelemic fluid. In another embodiment a device is used to deliver one or more substances, such as a drug, to an external surface of the fetal membranes.

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SYSTEM AND METHOD FOR TRANSFETAL (AMNION-CHORION) MEMBRANES TRANSPORT

FIELD OF THE INVENTION

This invention relates to medical devices, and more particularly to such devices for procedures and devices making use of ultrasound (US).

LIST OF PRIOR ART

The following is a list of prior art, which is considered to be pertinent for describing the state of the art in the field of the invention.

1. US 4,078,052 to Papahadjopoulos;
2. International Patent Application No. PCT IL2006/001404 to Barenholz et al;
3. US patent No. 4,780,212 to Kost;
4. Sundaram, J., Mellein B. R., and Mitragotri S., An experimental and theoretical analysis of ultrasound-induced permeabilization of cell membranes. Biophysical J. **2003** 84, 3087-3101.
5. US patent No. 5,458,140 to Eppstein, et al.
6. US patent No. 7,037,277 to Smith et al.
7. US patent No. 5,163,421 to Bernstein et al.
8. International Patent Application Publication No. WO01/70330 to Custer et al.

BACKGROUND OF THE INVENTION

Prenatal testing involves testing a fetus for the presence of various hereditary or spontaneous genetic disorders, such as Down syndrome. One of the most common procedures for detecting abnormalities before birth is amniocentesis in which a sample of the fluid surrounding the fetus (amniotic fluid) is obtained. In amniocentesis, after

anesthetizing an area of abdominal skin, a needle is inserted through the abdominal wall into the amniotic cavity. During the procedure, ultrasonography is performed so that the position of the fetus can be monitored and the needle guided into place without touching the fetus. Amniotic fluid is collected through the needle into a syringe, and the needle is then removed. Another fetal examination includes chorionic villus sampling (CVS). Both amniocentesis and CVS are invasive, and as such carry a small but definite risk to the mother and fetus. After amniocentesis, the chance of miscarriage due to the procedure is about 1 in 200.

Ultrasound has been used in a number of medical applications. Examples of clinical applications of ultrasound include imaging, stimulation of the healing of soft tissue, during topical application of a medication, and for enhancement of transdermal drug delivery into the circulatory system. In addition, ultrasound has also been used for selectively altering the permeability of cell membranes. This alteration is reversible and the effect can be controlled as to its extent and rate.

Further, a method for non-invasively monitoring the concentration of an analyte in an individual's body using ultrasound and for increasing permeability of a selected area of the individual's body surface have been described [5, 8]. The method makes use of chemical enhancers in combination with ultrasound sonication.

SUMMARY OF THE INVENTION

The present invention provides a system and method for enhancing the permeability of fetal membranes (amnion and chorion). The enhanced permeability may be utilized to withdraw substances from the gestational sac through the fetal membranes, or to introduce substances into the gestational sac through the fetal membranes, with out inserting a needle through the fetal membranes into the interior of the gestational sac.

The invention is based on the finding that the permeability of fetal membranes is increased by exposure to ultrasound sonication. Without being bound to a particular theory, it is believed that exposure of the fetal membranes to ultrasound sonication causes cavitation in the membranes and/or substances in contact with the fetal membranes, leading to micro-pore formation and enhanced permeability. It is further

believed that the micro-pores eventually reseal after the ultrasound sonication is terminated.

In one embodiment of the invention, a probe containing an ultrasound source is inserted through the vagina and positioned with the ultrasound sourcae in either the vagina or cervix. Ultrasound sonication is directed to a portion of the fetal membranes adjacent to the cervix, in order to enhance the permeability of the fetal membranes. In an application of the invention where a sample of a substance in the gestational sac, such as amniotic fluid or coelomic fluid, is to be obtained, the substance may be collected under suction into a receptacle. In an application where a substance is to be delivered into the gestational sac, the substance is delivered to the exterior surface of the permeabilized fetal membranes and allowed to diffuse into the interior of the gestational sac.

The ultrasound sonication may be performed using a continuous or pulsed sonication mode. The fetal membranes may be sonicated by a single ultrasound source or by two or more ultrasound sources sonicating the fetal membranes from different directions while being focused on the same region of the fetal membranes.

The ultrasound sonication will typically have intensity in a range between about 1 to 10 Watt/cm^2.

Thus, in one of its aspects, the present invention provides a system for trans-fetal membranes transport comprising:

(a) A source of ultrasound sonication configured to deliver ultrasound sonication to fetal membranes to enhance the permeability of the fetal membranes of a gestational sac; and

(b) a device selected from:

a device adapted to collect substances transported from an interior of the gestational sac to an exterior of the gestational sac; and

a device to deliver one or more substances to an external surface of the fetal membranes.

In another of its aspects, the invention provides a method for trans-fetal membranes transport comprising:

(c) delivering ultrasound sonication to the fetal membranes of a gestational sac to increase a permeability of the fetal membranes; and

(d) collecting substances transported from an interior of the gestational sac to an exterior of the gestational sac or delivering one or more substances to an external surface of the fetal membranes.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 shows a system for trans-fetal membranes transport according to one embodiment of the invention;

Fig. 2 shows a probe unit for use in the embodiment of fig. 1;

Figs. 3a and **3b** show the probe of Fig. 2 inserted in a vagina and a cervix;

Fig. 4 shows a system for trans-fetal membranes transport according to another embodiment of the invention;

Fig. 5 shows a probe unit for use in the embodiment of fig. 1;

Figs. 6a and **6b** show the probe of Fig. 2 inserted in a vagina and a cervix;

Figs. 7a and **7b** show a system for *in vitro* trans-fetal membranes transport;

Fig. 8 shows the effect of ultrasound sonication at the indicated intensities of postpartum human fetal membranes on membrane permeability; and

Fig. 9 shows the effect of ultrasound sonication at various intensities and a 50% duty cycle of postpartum human fetal membranes on the electrical conductivity of the membrane

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Fig. 1 shows a system generally indicated by **2** for transfetal membranes transport, in accordance with one embodiment of the invention. The system **2** may be used to generate transport through the fetal membranes from the interior of the

gestational sac to the exterior, for example, to obtain a sample of amniotic fluid or coelomic fluid.

The system **2** comprises a control unit **4** and a probe unit **6** which is attached to the control unit **4** via a harness **8.** The probe unit **6** has a handle **10**, a shaft **12**, a proximal end **13** and a distal end **15**. The shaft **12** may be rigid and permanently bent or curved to form a vaginal portion **16** and a cervical portion **18**. Alternatively, the shaft may be flexible so as to be bendable into an angled shape having a vaginal portion and a cervical portion.

Fig. 2 shows the probe unit **6** in greater detail. The cervical portion **18** comprises an ultrasound source **17** that emits ultrasound waves from the distal end **15** of the probe unit **6.** The ultrasound source **17** is contained in an outer sleeve **24** that extends along the length of the shaft **12**. The outer sleeve **24** is made from a biocompatible material such as Teflon or silicone. The outer sleeve **24** is attached to the handle **10** at a collar **25**. The outer sleeve is preferably detachable from the handle **10**, and is most preferably disposable. The probe unit **6** is also provided with a coupling medium delivery system which delivers an acoustic coupling medium to the distal end of the probe unit **6** for acoustic coupling of the ultrasound sonication to the body tissues, as explained below. A reservoir **22** is used to store an amount of an ultrasound coupling medium **24**. Depressing a spring-biased push button **28** drives a piston **29** to create an elevated pressure in the reservoir **22** via a conduit **26** that urges the coupling medium **24** to flow from the reservoir **22** out of the distal end **15** of the probe unit **12**.

The system **2** is also provided with a vacuum system that draws into the probe unit **6** substances released from the interior of the gestational sac to the exterior as a result of the ultrasound sonication of the gestational sac, as explained below. A vacuum pump **28** may be located in the control unit **4,** as shown in Fig. 1, or may be external to the control unit **4.** The vacuum pump **28** creates a negative pressure in a receptacle 38 in the sleeve **24** via a vacuum hose **32** in the harness **8,** and a connecting channel **34** in the handle **10**. A normally closed valve **36** in the connecting channel **34** is opened by depressing a spring biased push-button switch **37** when it is desired to create a negative pressure in the receptacle **38,** as explained below.

In an alternative embodiment (not shown) drawing of substances released from the gestational sac into the probe unit **6** utilizes a solution of high osmotic pressure that is applied to the external surface of the gestational sac. The high osmotic pressure solution draws amniotic and/or ceolomic fluid and dissolved or suspended substances across the fetal membranes by osmosis from the interior to the exterior of the gestational sac where the substances are collected in a receptacle.

The control unit contains a power supply **40** that is connected to the ultrasound transducer **17** via wires **44** in the harness **8** that connect with wires **45** in the probe unit **6.** Closing a switch **41** on the handle **10** activates the ultrasound source **17** to the power supply **40.** The control unit also contains a user input device, such as a key pad **42** that allows a user to input values of various parameters relating to the ultrasound sonication, such as intensity, pulse duration, pulse repetition rate or wavelength, as well as details of the individual being examined.

Figs. 3a and 3b show use of the system **2** to collect a body substance such as an amniotic fluid sample or a coelomic fluid sample from an individual **50**. The shaft **12** of the probe unit **6 is** introduced into the vagina **51** and positioned with the vaginal portion **16** in the vagina **51** and the cervical portion **18** in the cervix **52**. Positioning of the probe unit **6** in the body may be monitored by external ultrasonography to ensure proper placement of the probe unit **6** in the body. A small amount of coupling medium **24** is then expelled from the distal end **15** of the probe unit **6** by depressing the push-button **28**. The distal end **15** of the probe is then apposed to a portion of the fetal membranes **56** adjacent to the cervix **52** in order to ensure acoustic coupling of ultrasound sonication to the portion **56** of the fetal membranes. The ultrasound activation button **41** is then depressed to activate the ultrasound transducer **17**. Substances withdrawn from the gestational sac may be collected during and/or after the ultrasound sonication by depressing the push-button **29** to open the vacuum valve **36**. Ultrasound sonication **54** emitted from the ultrasound source **17** is directed to the portion of the fetal membranes **56** adjacent to the cervix **52**. As demonstrated below, exposure of the fetal membranes **56** to the ultrasound sonication **54** increases the permeability of the fetal membranes. The permeability of the fetal membranes **56** may be monitored during and after the sonication by measuring the conductivity of the membranes (not shown). Substances

passing out of the gestational sac as a result of the increased permeability, such as amniotic or coelomic fluid, are drawn into the distal end 15 of the probe unit 6 under the influence of the vacuum system and/or osmotic pressure when present, and are collected in the receptacle **24**. After collection of substances passing through the fetal membranes, the vacuum is turned off, and the probe unit **6** is removed from the body. Substances collected in the receptacle **38** are then removed from the receptacle **16** and are analyzed.

Fig. 4 shows a system generally indicated by **102** for transfetal membranes transport, in accordance with another embodiment of the invention. The system **102** may be used to transport substances such as drugs from the exterior of the fetal membranes into the gestational sac.

The system **102** comprises a control unit **104** and a probe unit **106** which is attached to the control unit **104** via a harness **108.** The probe unit **106** has a handle **110,** a shaft **112,** a proximal end **113** and a distal end **115.** The shaft **112** may be rigid and permanently bent, or may be bendable to form a vaginal portion **116** and a cervical portion **118.**

Fig. 5 shows the probe unit **106** in greater detail. The cervical portion **118** comprises an ultrasound source **117** that emits ultrasound waves from a distal end **115** of the probe unit **106.** The ultrasound source **117** is contained in an outer sleeve **124** that extends along the length of the shaft **112.** The outer sleeve **124** is attached to the handle **110** at a collar **125.** The outer sleeve is preferably detachable from the handle **110,** and is most preferably disposable. The probe unit **106** is also provided with a coupling medium delivery system which delivers an acoustic coupling medium to the distal end of the probe unit **106** for acoustic coupling of the ultrasound sonication to the body tissues, as explained below. A reservoir **122** is used to store an amount of an ultrasound coupling medium **124.** Depressing a spring-biased push button **128** drives a piston **129** to create an elevated pressure in the reservoir **122** via a conduit **126** that urges the coupling medium **124** to flow out from the reservoir **122** though the delivery tube **126** to the distal end **115** of the probe unit **112.**

The system **102** is provided with a delivery system for delivering one or more substances, such as drugs, to the external surface of the gestational sac. The one or more

substances **160** are stored in a reservoir **165.** Depressing a spring-biased push button **168** drives a piston **169** to create an elevated pressure in the reservoir **165** via a conduit **166** that urges the substances to flow from the reservoir **165** out of the distal end **115** of the probe unit **112.**

The control unit contains a power supply **140** that is connected to the ultrasound transducer **117** via wires **144** in the harness **108.** Closing a switch **141** on the handle **110** activates the ultrasound source **117.** The control unit also contains a user input device, such as a key pad **142** that allows a user to input values of various parameters relating to the ultrasound sonication, such as intensity, pulse duration, pulse repetition rate or wavelength, as well as details of the individual being examined.

Figs. 6a and 6b show use of the system **102** to deliver the one or more substances **160,** such as a drug, into a gestational sac of an individual **150.** The shaft **112** of the probe unit **106** is introduced into the vagina **152** and is positioned with the vaginal portion **116** in the vagina **151** and the cervical portion **118** in the cervix **152.** A small amount of coupling medium **124** is then delivered to the distal end **115** of the probe unit **106** by depressing the push-button **128.** The distal end **115** of the probe is then apposed to a portion of the fetal membranes **156** adjacent to the cervix **152** in order to ensure acoustic coupling of ultrasound sonication to the portion **156** of the fetal membranes. The ultrasound activation button **141** is then depressed to activate the ultrasound source **117.** The one or more substances **136** are delivered to the distal end **115** of the shaft **112** by depressing the push-button **168,** during or after the ultrasound sonication. Ultrasound sonication **154** emitted from the ultrasound source **117** is directed to the portion of the fetal membranes **156** adjacent to the cervix **52.** As demonstrated below, exposure of the fetal membranes **156** to the ultrasound sonication **154** increases the permeability of the fetal membranes. The permeability of the membranes **156** may be monitored during and after the sonication by measuring the electrical conductivity of the membranes (not shown). The substances **160** delivered to the distal end **115** of the shaft **112** are available to diffuse across the fetal membranes as a result of the increased permeability. After delivery of the substances **160,** the probe unit **106** is removed from the body.

In one embodiment, the ultrasound sonication has a frequency of between about 20 kHz to about 3MHz. In a preferred embodiment the ultrasound sonication has a frequency between about 20kHz and about 500kHz, and more preferably between about 20kHz and 100kHz. This range is referred to at times by the term "*low frequency ultrasound sonication*" (LFUS). In one embodiment, continuous ultrasound sonication for about 5 sec to about 30 min, more preferably, from about 30 sec to about 10min, is used.

Experimental results

Example 1 – *In vitro* permeability of amniotic membrane

The permeability of postpartum human fetal membranes (obtained from Hillel Yaffe Medical Center, Israel) upon exposure to ultrasound was determined. The experimental set-up used is shown schematically in Fig. 7. As shown in Fig. 7a, fetal membranes **180** (a piece of a gestational sac) were mounted on a glass vertical diffusion cell **182** with the maternal side facing a donor compartment **186**. A receiver compartment **184** was filled with phosphate Buffer Saline (PBS) **185**. The donor compartment **186** was filled with an ultrasound coupling medium **188** comprising 1% Sodium Dodecyl Sulphate (SDS) in phosphate Buffer Saline (PBS). The tip of a 1 cm (diameter) ultrasound transducer (VCX-400 (Sonics & Materials, Newtown, CT) **190** was immersed in the coupling medium **188** at a distance of 1 mm from the membranes **180**. The membranes were then sonicated with ultrasound sonication at a frequency of 20 KHz for a duration of 10 minutes, and at various intensities as indicated below and with a duty cycle of 50% (0.5 sec on, 0.5 sec off). In control experiments, the ultrasound sonication was omitted.

After 10 minutes of the pulsed sonication, the coupling medium **188** was removed from the donor compartment **186**, the membranes **180** were removed and washed with PBS, and the PBS **185** was removed from the receiver compartment **184**. Then, as shown in Fig. 7b, the sonicated membranes **180** were remounted on the diffusion cell **182**, this time with the maternal surface facing the receiver compartment 184, and fresh PBS **192** was added to the receiver compartment **184** together with a magnetic stirring bar **196**. 2 ml of Dextran (average molecular weight 40 KDa)

conjugated to the fluorescent label FITC (Fluorescein Isothiocyanate-Dextran)) **194** at a concentration of 12.5 μM in PBS was added to the donor compartment **186**. From this point, the diffusion cell **182** was protected from light, in order to prevent fluorescent bleaching of the fluorescent label. 1 ml samples were withdrawn from the receiver compartment **186**, at different times and analyzed for the concentration of the fluorescent label.

From the rate of increase in the concentration of the fluorescence in the receiver compartment **184**, the extent of permeability enhancement of the membrane, in comparison to a control membrane not sonicated with ultrasound sonication was calculated. Fig. 8 shows the enhancement in permeability of the membrane, compared to the non-sonicated control, for the different ultrasound intensities used. An optimal effect was observed at an intensity of about 2.5 Watts/cm^2 (at a duty cycle of 50%).The decline in permeability at higher intensities may due to a gas decoupling effect on the surface of the ultrasound probe.

During the ultrasound sonication, the electrical conductivity of the postpartum membranes **180** was determined at five minute intervals. Fig. 9 shows the enhancement in conductivity of the membranes as a function of time during ultrasound sonication at the intensities indicated . At intensity of 4.3 Watts/cm^2 (at a duty cycle of 50%) and above, the membrane ruptured after 10 to 30 minutes of irradiation.

CLAIMS:

1. A system for trans-fetal membranes transport comprising:

(a) A source of ultrasound sonication configured to deliver ultrasound sonication to fetal membranes to enhance the permeability of the fetal membranes of a gestational sac; and

(b) a device selected from:

a device adapted to collect substances transported from an interior of the gestational sac to an exterior of the gestational sac; and

a device to deliver one or more substances to an external surface of the fetal membranes.

2. The system according to Claim 1 comprising a probe unit containing the ultrasound source adapted to be inserted into a vagina.

3. The system according to Claim 1 wherein the probe unit is adapted to be inserted into a cervix.

4. The system according to Claim 1 wherein the probe unit is configured to deliver an acoustic coupling material to a distal end of the probe unit.

5. The system according to Claim 1 comprising a device adapted to collect substances transported from an interior of the gestational sac to an exterior of the gestational sac.

6. The system according to Claim 5 wherein the device is adapted to collect substances transported from an interior of the gestational sac to an exterior of the gestational sac comprises a receptacle collecting substances transported from the interior of the gestational sac to an exterior of the gestational sac .

7. The system according to Claim 5 or 6 wherein the device is adapted to collect substances transported from an interior of the gestational sac to an exterior of the gestational sac comprises a vacuum system drawing substance away from the fetal membranes.

8. The system according to Claim 5 or 6 wherein the device is adapted to collect substances transported from an interior of the gestational sac to an exterior of the gestational sac comprises a high osmotic solution.

9. The system according to Claim 1 comprising a device to deliver one or more substances to an external surface of the fetal membranes.

10. The system according to Claim 9 wherein the device to deliver one or more substances to an external surface of the fetal membranes comprises a piston.

11. The system according to any one of the previous claims further comprising a control unit.

12. The system according to any one of the previous claims further comprising an electrical conductivity system measuring electrical conductivity of the fetal membranes.

13. A method for trans-fetal membranes transport comprising:

(a) delivering ultrasound sonication to the fetal membranes of a gestational sac to increase a permeability of the fetal membranes; and

(b) collecting substances transported from an interior of the gestational sac to an exterior of the gestational sac or delivering one or more substances to an external surface of the fetal membranes.

14. The method according to Claim 13 wherein the ultrasound sonication is delivered using an ultrasound source inserted into a vagina.

15. The method according to Claim 13 wherein the ultrasound sonication is delivered using an ultrasound source inserted into a cervix.

16. The method according to Claim 13 further comprising delivering an acoustic coupling material between the ultrasound source and a body tissue.

17. The method according to Claim 13 further comprising collecting one or more substances transported from an interior of the gestational sac to an exterior of the gestational sac.

18. The method according to Claim 17 wherein the substances are collected in a receptacle positioned in a vagina or a cervix.

19. The method according to Claim 17 or 18 further comprising drawing substance away from the fetal membranes by a vacuum.

20. The method according to Claim 17 or 18 further comprising drawing substance away from the fetal membranes by a high osmotic solution.

21. The method according to any one of Claims 17 to 20 wherein the one or more substances is an amniotic fluid or a coelomic fluid.

22. The method according to Claim 13 comprising delivering one or more substances to an external surface of the fetal membranes.

23. The method according to Claim 21 wherein the one or more substances are delivered to an external surface of the fetal membranes under pressure.

24. The method according to any one of Claims 13 to 23 wherein a substance is transported across the fetal membrane by diffusion.

25. The method according to any one of Claims 13 to 24 further comprising monitoring electrical conductivity of the fetal membranes.

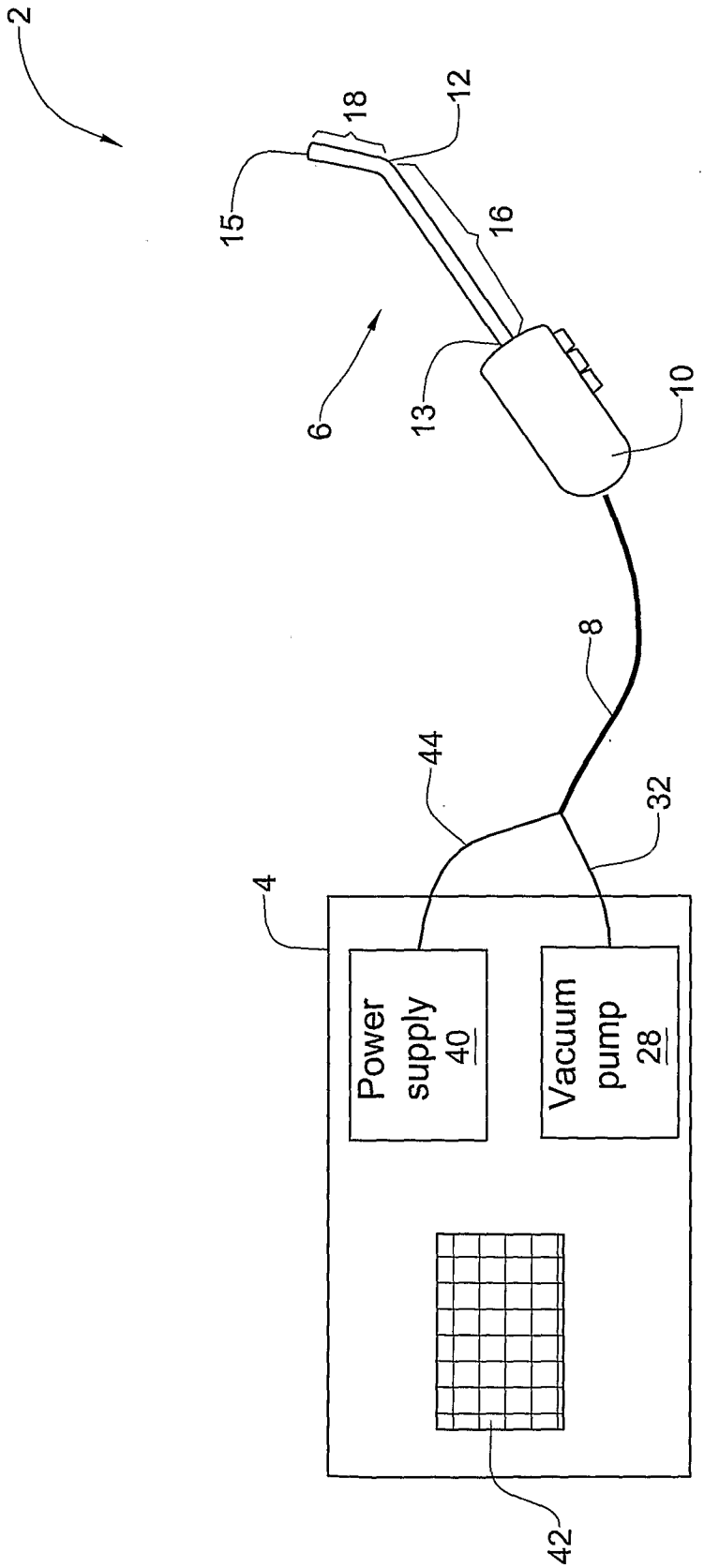

FIG. 1

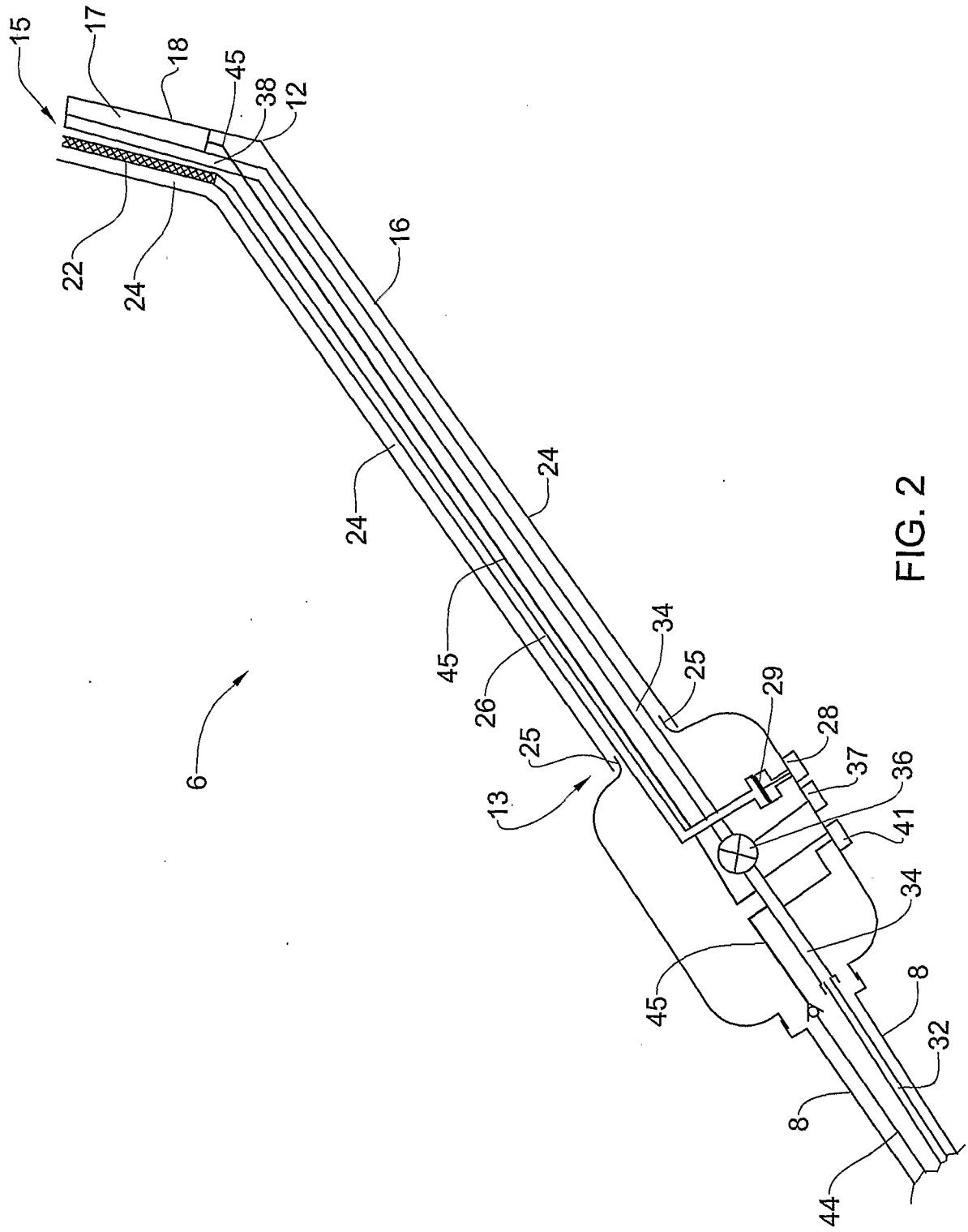
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FIG. 2

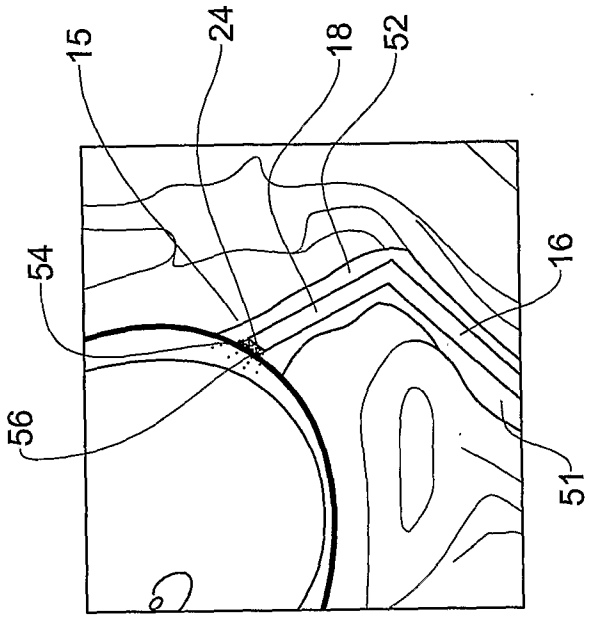


FIG. 3b

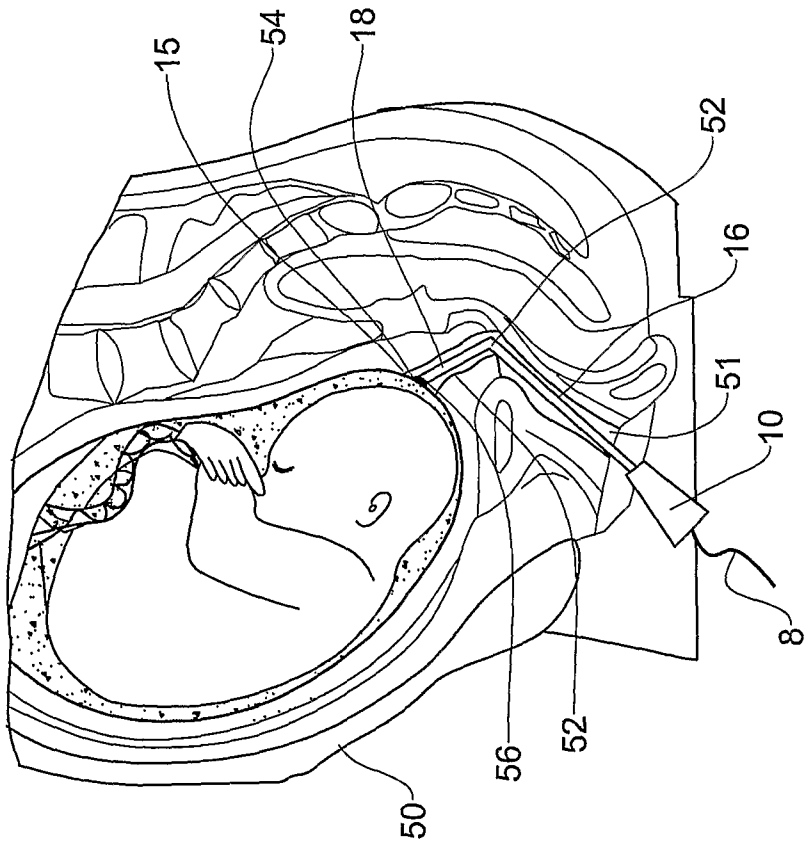
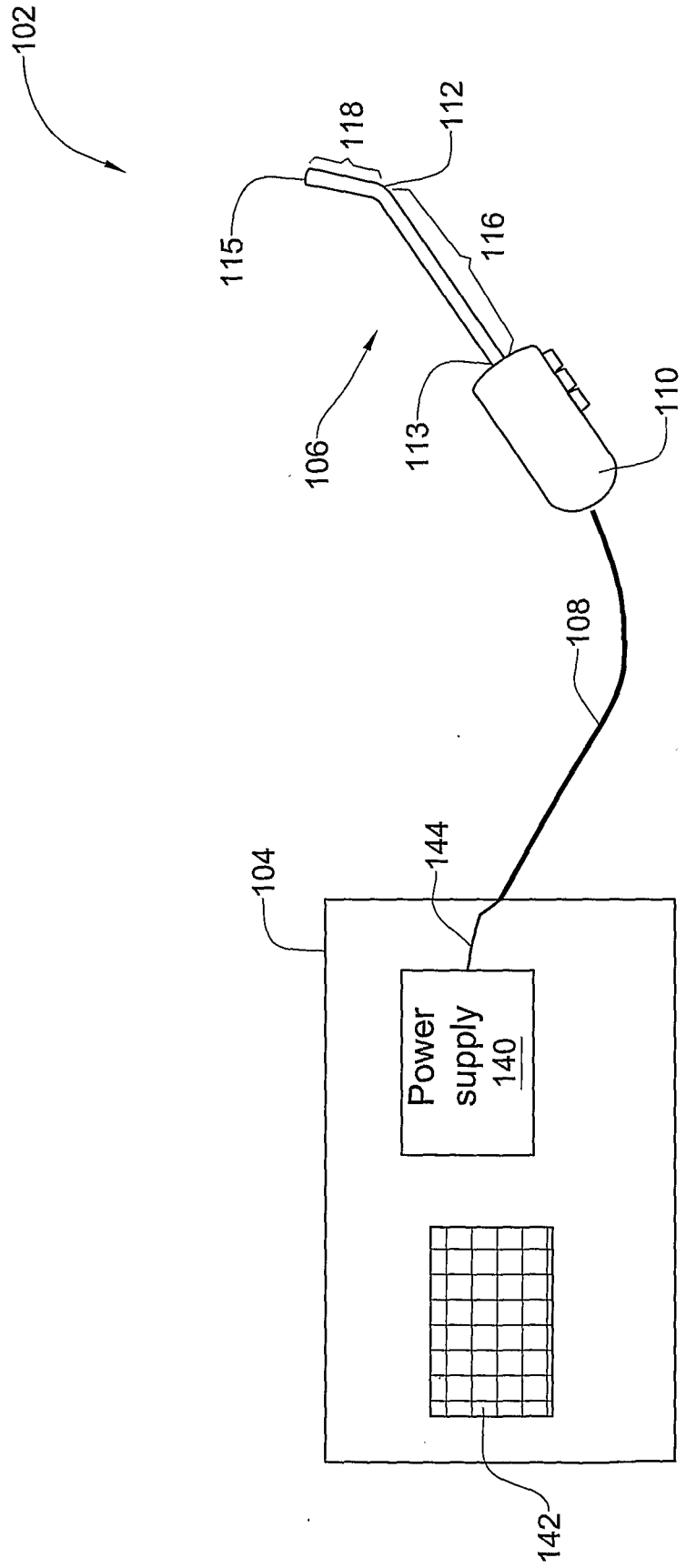


FIG. 3a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Power supply 140
142

FIG. 4

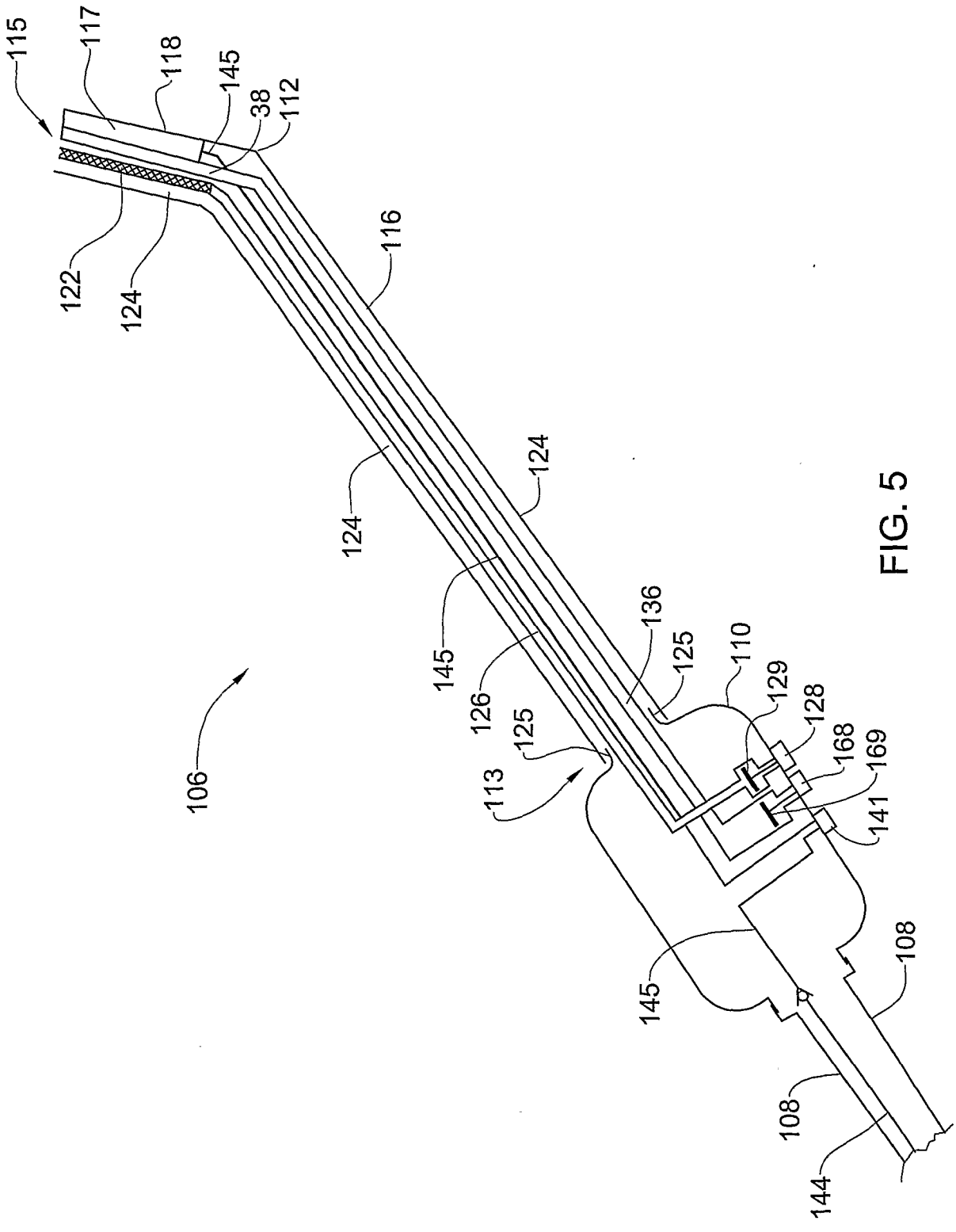
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FIG. 5

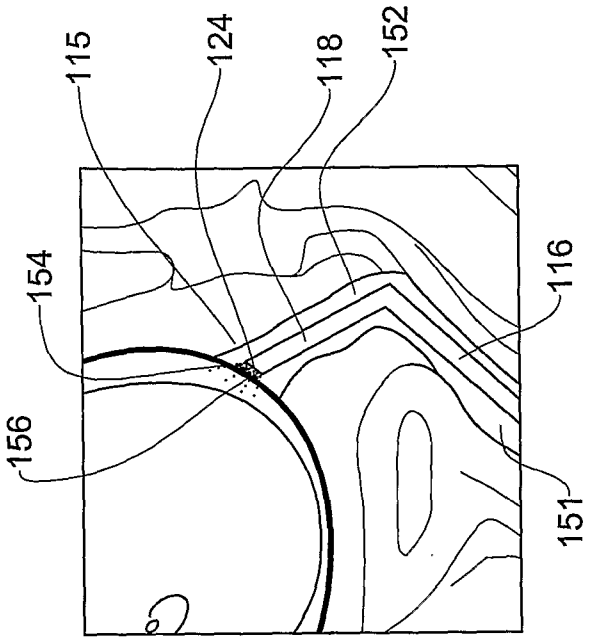
115
124
118
152
154
116
156
151

FIG. 6b

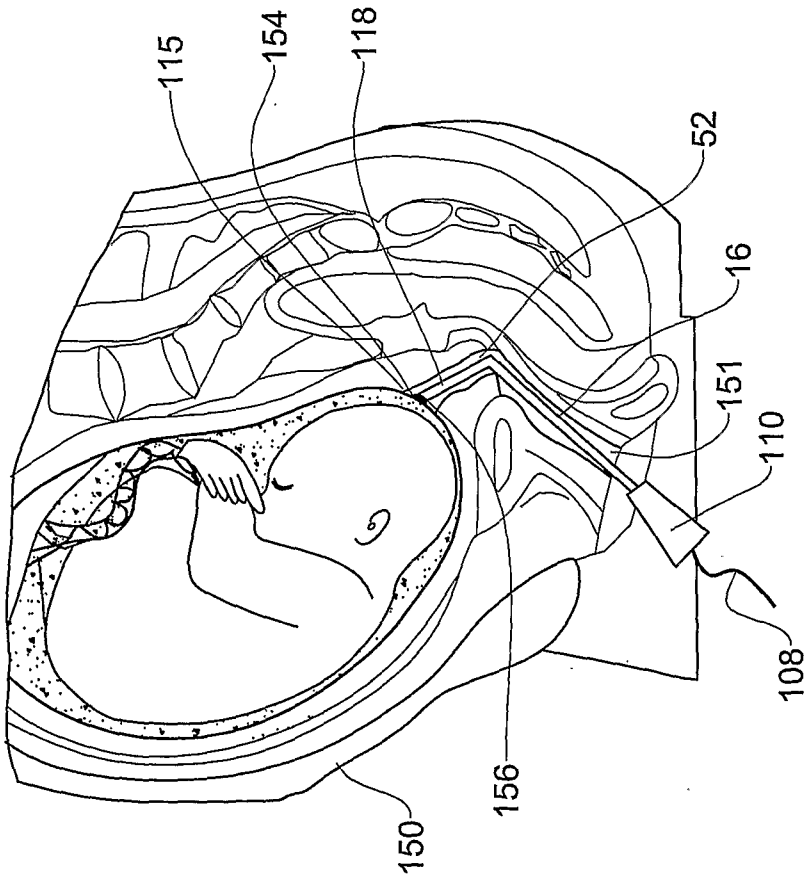
115
154
118
52
16
151
110
108
156
150

FIG. 6a

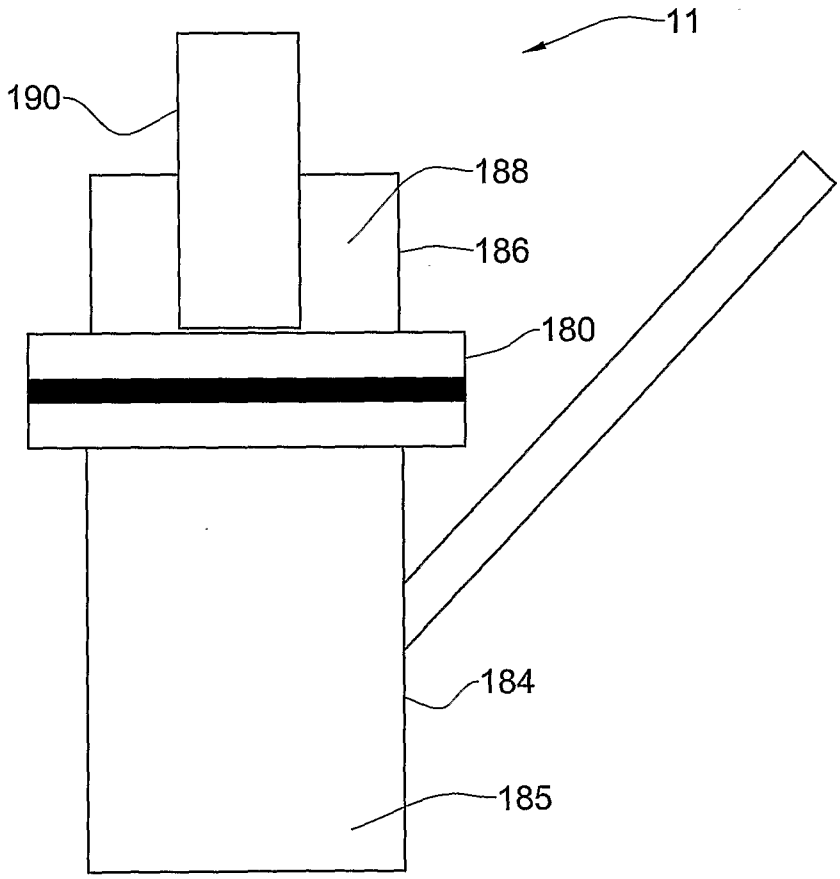

FIG. 7a

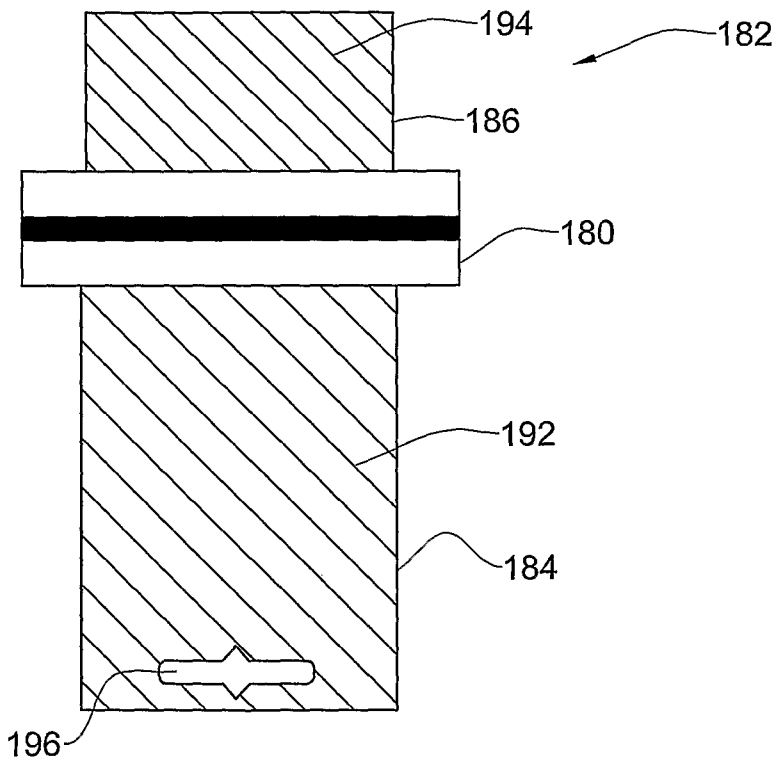

FIG. 7b

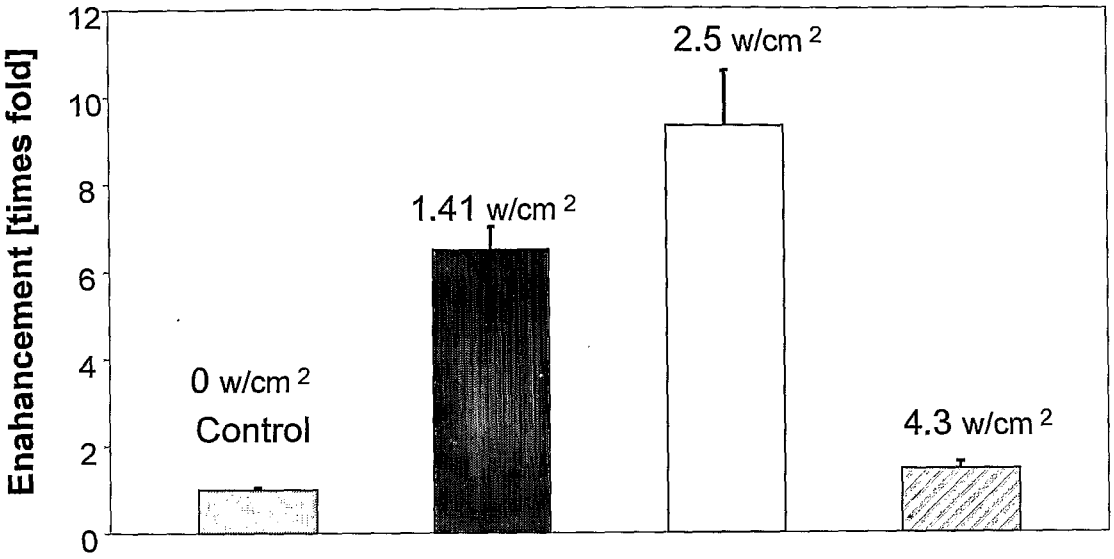
Enahancement [times fold]
12
10
8
6
4
2
0
0 w/cm 2
Control
1.41 w/cm 2
2.5 w/cm 2
4.3 w/cm 2

FIG. 8

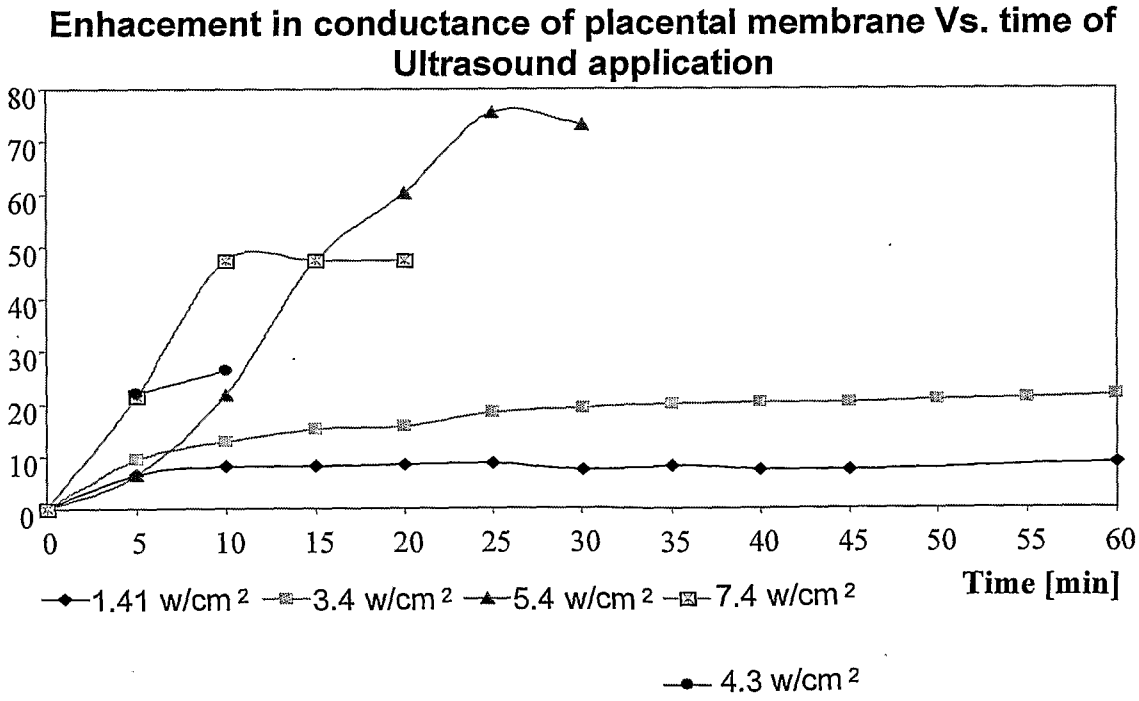
Enhacement in conductance of placental membrane Vs. time of Ultrasound application
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
55
60
Time [min]
1.41 w/cm 2
3.4 w/cm 2
5.4 w/cm 2
7.4 w/cm 2
4.3 w/cm 2

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2007/000716

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M37/00 A61B10/00

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)
A61M A61N A61B

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 practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/058530 A (IGER YONI [IL]) 1 August 2002 (2002-08-01) page 22, line 16 - line 22; figure 9	1-6,9,11
X	WO 98/48711 A (EKOS CORP [US]) 5 November 1998 (1998-11-05) page 2, line 8 - line 18 page 5, line 1 - line 5 page 9, line 7 - line 9; figure 1a	1-4,9-11

☐ 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

"E" earlier document but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 October 2007	17/10/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	MAYER-MARTENSON, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2007/000716

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13-25
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgeryRule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2007/000716

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02058530 A	01-08-2002	AU 2002225320 A1	06-08-2002
		EP 1389064 A2	18-02-2004
		US 2005075620 A1	07-04-2005
WO 9848711 A	05-11-1998	NONE	