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(54) **DRUG DELIVERY SYSTEMS AND METHODS FOR MODULATING THE FETAL ENVIRONMENT AND PREGNANCY PROCESS**

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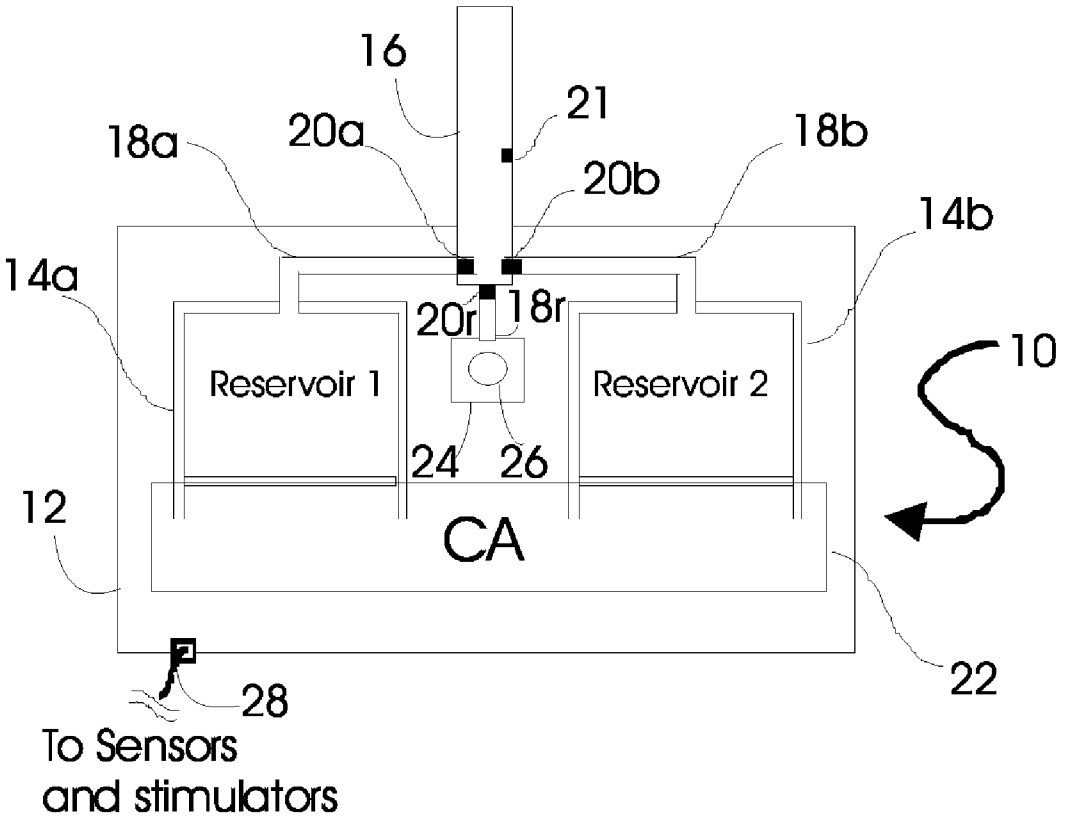
(57) **ABSTRACT**

Systems and Methods are described for treatment of fetal disorders, promotion of fetal health, and extension of the pregnancy period. A drug delivery system (DDS) can perform both bolus and continuous delivery of substances in accordance with sensed data reflecting the current state of a fetus. The methods and systems for promotion of healthy pregnancy and treatment of a developing fetus can alter the drug delivery, by evaluating the sensed data with respect to the age or physical characteristics of the fetus and/or mother.



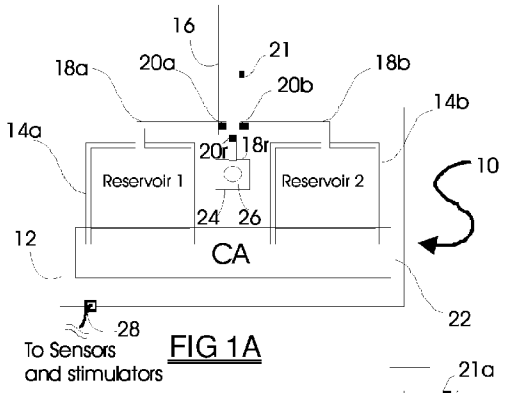


FIG 1A

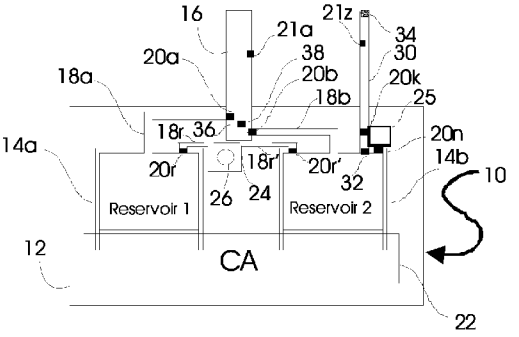


FIG 1B

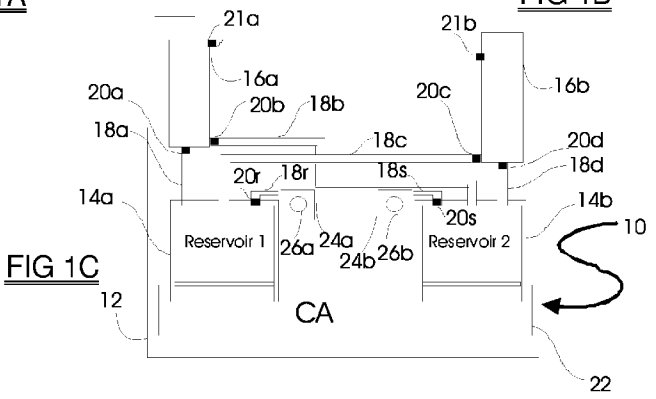


FIG 1C

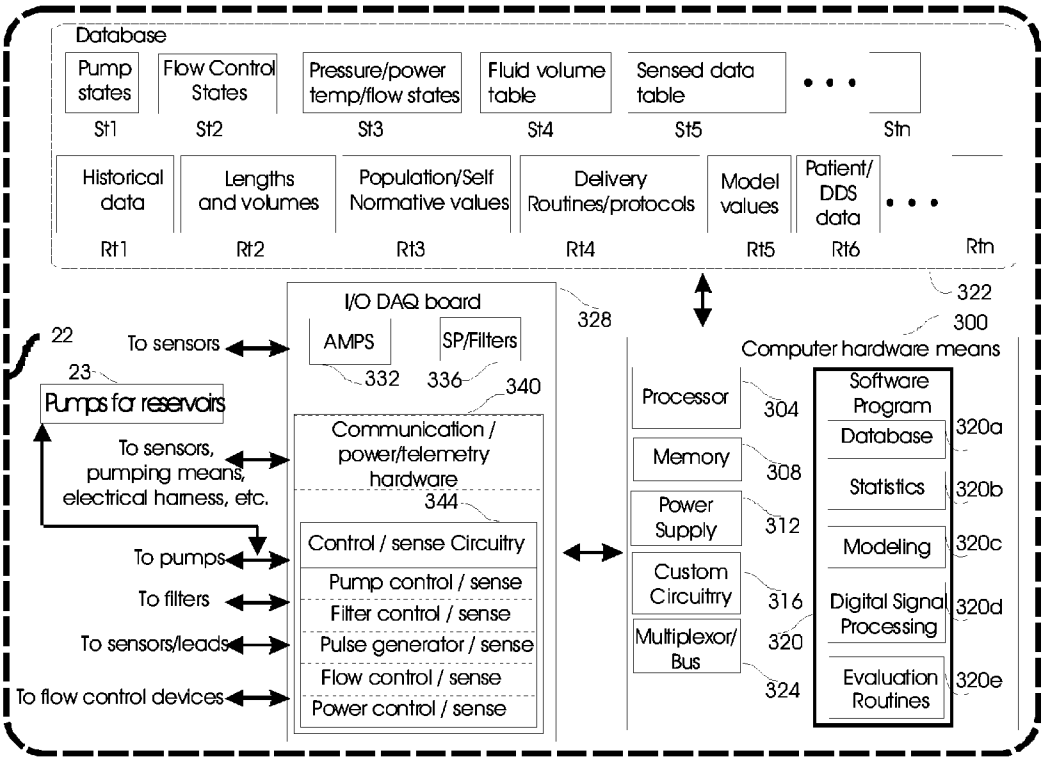

Database
Pump states
Flow Control States
Pressure/power temp/flow states
Fluid volume table
Sensed data table
St1
St2
St3
St4
St5
Stn
Historical data
Lengths and volumes
Population/Self Normative values
Delivery Routines/protocols
Model values
Patient/ DDS data
Rt1
Rt2
Rt3
Rt4
Rt5
Rt6
Rtn
322
300
Computer hardware means
I/O DAQ board
328
AMPS
SP/Filters
332
336
340
22
To sensors
23
Pumps for reservoirs
To sensors, pumping means, electrical harness, etc.
Communication / power/telemetry hardware
344
To pumps
Control / sense Circuitry
Pump control / sense
To filters
Filter control / sense
To sensors/leads
Pulse generator / sense
Flow control / sense
To flow control devices
Power control / sense
Processor
304
Memory
308
Power Supply
312
Custom Circuitry
316
Multiplexor/ Bus
320
324
Software Program
Database
320a
Statistics
320b
Modeling
320c
Digital Signal Processing
320d
Evaluation Routines
320e

FIG 2

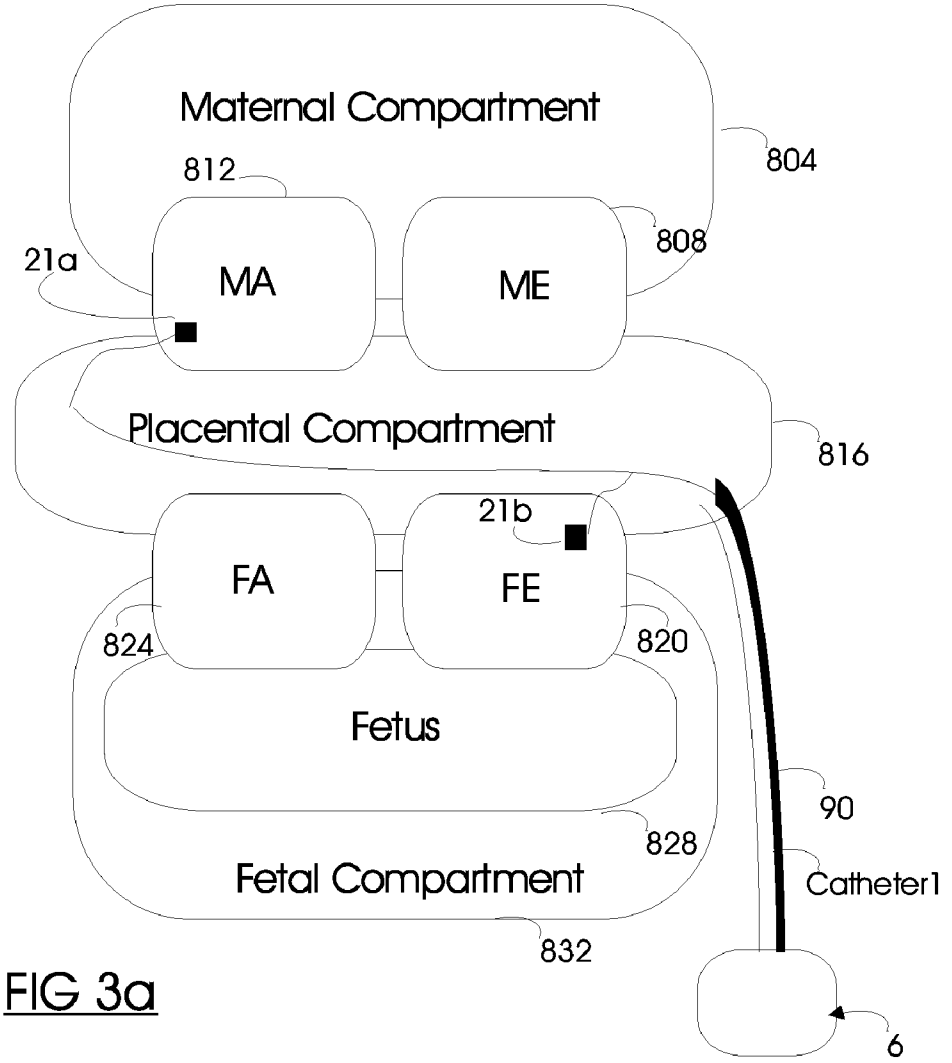
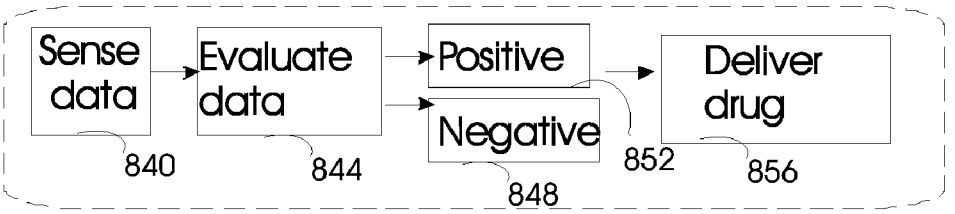

Maternal Compartment
804
812
808
21a
MA
ME
Placental Compartment
816
21b
FA
FE
824
820
Fetus
90
828
Fetal Compartment
Catheter1
832
6

FIG 3a

FIG 3b


Sense data
Evaluate data
Positive
Negative
Deliver drug
840
844
848
852
856

DRUG DELIVERY SYSTEMS AND METHODS FOR MODULATING THE FETAL ENVIRONMENT AND PREGNANCY PROCESS

[0001] This application claims the benefit of Provisional Application No. 60/587,870 filed on Jul. 15, 2004, which claims priority of Provisional Application No. 60/488,133, filed on Jul. 16, 2003, and Provisional Application No. 60/574,195, filed on May 25, 2004, and further claims the benefit of U.S. patent application Ser. No. 10/893,414 filed on Jul. 16, 2004, all herein incorporated by reference.

[0002] The present invention relates to modulation of the fetal environment and more particularly to treatment of fetal disorders, disorders of pregnancy, medical devices for modulation of the fetal environment, and more particularly to partially or completely implantable drug delivery systems which can deliver one or more stored substances prior to, or during, pregnancy and labor.

BACKGROUND

[0003] Patients often require continuous or bolus administration of medications which can be delivered at regularly occurring times, times dictated by a treatment regimen, in response to a patient's request, or in response to a biological/physiological event. An increasing assortment of implantable drug delivery systems are being designed to treat patients who may use the drug delivery technology to dispense therapeutic agents to treat medical conditions such as diabetes, arthritis, cancer, movement disorders such as spasticity, heart conditions and irregularities, various neurological or psychiatric conditions, disorders of the digestive system, autoimmune disorders, and many other medical conditions and disorders as well. Medical drug delivery technology can be also be used to modulate the process of pregnancy, by delivering drugs to the mother, fetus, or both.

[0004] U.S. Pat. No. 5,980,508 describes a system that allows for multiple drugs, multiple doses, and continuous or pulsatile/interval delivery. However, the technology is suboptimal because the concentration and delivery system must be configured prior to the implantation of the pump, rather than being dynamically adjusted once implanted, based upon the needs of the patient. Although some fetal drug delivery may occur according to a predetermined regimen, for example, increasing a dose at later times in the pregnancy period, in one embodiment of the current invention, the drugs delivery can be determined, for example, by evaluation of sensed data.

[0005] Drug delivery systems containing sensors and multiple pumps have been described which allow the delivery of drug to occur in response to a physiological event. For example, U.S. Pat. No. 6,066,163, describes an adaptive neurostimulation system which contains a reservoir infusion apparatus which stimulates the central nervous system with drugs in response to abnormal states which are sensed by one or more sensors. U.S. Pat. No. 5,062,841 discloses an insulin pump which can be used to pump insulin directly into the bloodstream in response to blood glucose levels. U.S. Pat. No. 5,433,701 discloses an active ocular pressure control device which includes a pump which is selectively operated in response to a control signal from a pressure sensor. However, this art relates primarily to algorithms and methods of using the sensed data to control the pumping/drug delivery system and dispense an appropriate drug to an adult, and do not disclose drug delivery to a fetus, and does not disclose delivery based upon data sensed from the mother, from the fetus, or both.

[0006] It has become an increasingly common practice in obstetrics to evaluate the well being of the baby while it is still in utero. This practice, often termed anterpartum testing, has been extensively practiced since the early 1970s on certain high risk obstetrical patients. One of the uses of anterpartum testing is to determine how well the placenta is supplying the needed oxygen and nutrients to the growing fetus, and removing fetal wastes therefrom. Fetal monitoring during labor is one of the most standard clinical antepartum practices. Its purpose is to identify abnormal events, particularly fetal oxygen deficiency. Often the fetal heart rate is monitored by determining the interval between successive R-wave peaks in the ECG signal since these peaks are by far the most pronounced portion of a normal ECG signal. US20040015066 describes fetal scalp electrodes suitable for use in producing an electrocardiogram (ECG) signal during delivery of the fetus. This art does not describe providing automatic (e.g., closed-loop), or semi-automatic intervention in the form of drug delivery, based upon or in response to an evaluation of the ECG signal. The current art is an advantage as it discloses such methods.

[0007] In addition to ECG monitoring, collecting blood from an infant during the birthing process is employed extensively when there is an indication of risk that an infant is not receiving an adequate supply of oxygen, for example, due to strangulation of an umbilical chord or premature separation of the placenta. Fetal blood sampling may involve passing an amnioscope through the birth canal to contact the fetal presentation. A lance, or similar incising instrument may then be introduced through the amnioscope to make an incision (e.g, see U.S. Pat. No. 6,423,011). Alternatively, fetal blood oxygenation can be monitored using a photodetector as described in U.S. Pat. No. 5,419,322 and US2005033130. An optical cell (and spectral analyzer) can be used for detecting the presence and concentration of meconium and/or blood in amniotic fluid, as is described in EP0581450. However, such monitoring is not incorporated as a step in automatic, or semi-automatic intervention in the form of drug delivery.

[0008] Extensive and automatic fetal monitoring, has been described as in WO2004012598 and WO2005025419, which provide monitoring of abdominal and fetal movements using in-utero ultrasound based techniques and physiological fetal-ECG measurements. For example, monitoring an expectant mother's abdominal movements within the range of 8-25 Hz can be assumed to be largely the result of fetal activity as opposed to uterine contractions, respiratory movements, and maternal posture movements. These two types of measurements can be combined for greater precision. Further, US2003187364 utilizes the fetal-ECG measurements to determine if there is a risk of developing a permanent neurological condition. A likelihood that the ECG-condition of the fetus belongs to a class in a group of classes, where each class in the group of classes is associated with a pre-defined fetal condition, is used to provide a risk index. However, again, automatic or semi-automatic intervention using drug delivery is not discussed, and is not provided in response to this risk index.

[0009] Additionally, U.S. Pat. No. 6,024,701, entitled "Monitor for estimating placenta and fetus well being"

describes method and system for evaluating the condition of the placenta in pregnant women and the well being of the fetus and/or the mother by using physiological parameters which are evaluated using system identification methods. The invention aims to estimate the functionality and well being of the placenta and fetus from the second trimester onward. In one preferred embodiment, the physiological signals to be monitored may be selected from the group consisting of ECG, BP, PO2, PCO2, blood flow, blood velocity, blood volume, heart rate, systolic blood pressure, diastolic blood pressure, systolic/diastolic blood pressure ratio, resistance index, pulsatility index, thermal index and other Doppler flow indexes. While monitoring may be used to detect conditions associated with fetal hyperinsulinemia, preeclampsia, and other disorders, the methods and systems of this prior art do not suggest any type of automatic or semi-automatic treatment protocol which relies upon drug delivery. Further, no mention of evaluating the data with respect to self- or population-normative values is described.

[0010] Pharmaceutical intervention to promote fetal health, has be proposed. For example, RU2188643 describes administering a cardiotropic metabolic therapeutic complex comprising cardiac glycoside, potassium and magnesium ions, insulin per 400.0 of 5% glucose solution and calcium antagonist preparation in tablet form. The treatment course is 10-14 days long and provides improved prophylaxis for central nervous system injuries and prolonged pregnancy to achieve viable fetus time. However, the drug administration is not directed to the fetus, and is not altered based upon the developmental stage, or other physical attribute of the fetus, and does not occur, or become modified, in response to sensed data.

[0011] The prior art mainly focuses on the later segment of the pregnancy process which surrounds labor. The systems and methods of the current invention can be used to promote a healthy intrauterine environment prior to, and during pregnancy and labor. The consequences of an unfavorable intrauterine environment can extend throughout the entire life of an individual, may be irreversible, and are of major importance worldwide. While fetal growth and development are determined primarily by the genetic potential of the fetus, these can be strongly influenced by environmental factors, which can exert stimulatory or inhibitory effects. When the fetal environment is abnormal, the fetus may not develop normally, and while some compensatory mechanisms may be available, these compensations may also lead to abnormal development and medical disorders. In order to obtain its supply of nutrients, the fetus depends on the nutritional status of the mother and the capacity of the placenta to transport these nutrients to the fetus. The ability of the fetus to utilize these nutrients may also depend upon the availability of other compounds (e.g, a balanced mixture of amino acids may be needed to build proteins). The fetus also has its own growth factors, which influence growth and differentiation. Normal fetal growth is the result of an equilibrated interplay between these different factors. Any imbalance between these factors can result in disorders such as fetal growth restriction (microsomia) or fetal overgrowth (macrosomia). Abnormalities in fetal growth and development which are related to an abnormal intrauterine environment, or which are related to problems in the genetic code, anatomy, or metabolism of the fetus itself, can be treated using the drug delivery systems and methods described herein.

[0012] The systems and methods of the current invention can be used in promoting healthy pregnancy and fetal wellbeing, reducing the risk of preterm labor or fetal insufficiency, reducing the likelihood of, or treating, infections and bacterial growth, compensating for metabolic or other disorders of the mother or fetus, and in various other medical applications. When a drug delivery system is used for obstetric applications, a portion of its components can be implanted in areas such as the birth canal, womb, or in a proximal area of the body cavity, and some components, such as reservoirs, can exist outside of the body.

[0013] It is an object of the present invention to provide drug delivery systems and methods to obviate or mitigate at least some of the above presented disadvantages of the prior art, and thereby provide improved and desired modulation of the development of the fetus, the environment of the fetus, and the pregnancy and labor process.

SUMMARY

[0014] The drug delivery systems of the present invention can provide for mixing various drugs in an optimally controlled manner, use flow controllers to guide multiple drugs into a single or into multiple catheters, enable a single lumen catheter to treat a specific region with several drugs, allow for dilution of a concentrated drug in order to both increase the time between refilling and also to provide any concentration of a drug that might be desired, provide for using a buffer fluid to deliver exact amounts of several drugs from the same catheter or to separate several drugs within a single catheter, and can use external fluid present in the human body either as a diluent or buffer fluid. The drug delivery system (DDS) can perform both bolus and continuous delivery of substances, and enable the measured delivery of any one of several drugs to one or more distal locations at independently programmable rates. New methods for using the DDS embodiments described herein (as well as for using generic drug delivery systems which are commercially available) in the promotion of healthy pregnancy and treatment of a developing fetus are described.

[0015] According to one embodiment of the DDS, there is provided an implantable drug delivery device for controlling a dispensing of a fluid drug to an internal target site of a patient, the device comprising: a first reservoir for storing a first fluid; an input port in fluid communication with the first reservoir; an output port in fluid communication with the first reservoir; a flow control system for controlling the transfer of the first fluid between the respective ports and the first reservoir, the flow control system having at least one flow controller; and a flow control module for directing the at least one flow controller to direct the flow of the first fluid between a selected one of the ports and the first reservoir.

[0016] According to a further aspect there is provided one of several catheter assemblies such as a dual lumen catheter, a variable volume mixing chamber, as are described in U.S. patent application Ser. No. 10/893,414 filed previously by the inventor and incorporated by reference herein, to provide for a drug delivery system which is capable of controlled delivery of both bolus and continuous flow of one or more substances, which may be substantially mixed or which may be presented sequentially, and which are delivered through a single catheter or through multiple catheters.

[0017] It is another feature of the present invention to provide for a drug delivery system which is capable of

delivering more than one concentration of a substance, and perform dose titration by modifying either the concentration, or rate of dispensing, or both.

[0018] It is another feature of the present invention to provide for a drug delivery system which draws upon and utilizes a biological fluid available from the mother, such as amniotic fluid, rather than, or in addition to, a synthetic fluid, as an active drug, a buffer fluid, or a diluent, and thereby decreases the need for filling the drug delivery system from a source outside the body.

[0019] It is another feature of the present invention to provide for an implantable drug delivery system which is capable of delivering more than one substance through each of one or more specific catheters.

[0020] It is a further feature of the present invention to facilitate a healthy birth process by delivering drugs to achieve for example: increasing the chance for conception, increasing the health of a developing fetus, assisting in normalizing fetal-placental flow or in compensating for abnormal flow, sensing the properties of the fluid in the vessels of the umbilical cord and using the properties of the fluids of the umbilical cord to guide the DDS dispensing or pumping operations, decreasing the risk of illness of the fetus, providing nutrients in response to lack of nutrients provided by the maternal sources, decreasing the unwanted effects of maternal exposure to substances that could be harmful to the fetus, in providing gene or germ therapy to the fetus, delivering therapeutic drugs in order to decrease the variability of the substances provided by the mother (e.g., as may occur when the mother has a metabolic disorder), decreasing the risk of infection or other viral or bacterial abnormality in the womb, decreasing the probability of premature labor, and assisting in extending the labor period.

[0021] Another feature of the present invention utilizes drug delivery to increase the likelihood of optimizing the health of the fetus. The drug delivery is directly to the fetus rather than to the mother, via a uterine target such as for example, the supporting vasculature, the placenta, or the vessels of the umbilical cord.

[0022] Another feature of the present invention uses a method which senses concentrations of substances in the umbilical artery or vein, the placenta, other structure of the fetal compartment, and evaluates this sensed data, and delivers drugs based upon this evaluation to a target in the fetal compartment or in the placenta in order to achieve a desired therapeutic result and/or in order to protect against a substance that could affect the fetus.

[0023] Another feature of the present invention uses a method which senses data from at least two sensors in the fetal compartment, in the maternal compartment, or in both compartments, and creates an input/output ratio or other index (which may be based upon a model) on which drug delivery to a uterine target or directly to the fetus, may be based.

[0024] Another feature of the present invention uses a method which senses intra-uterine, placental, umbilical (e.g., umbilical vein), amniotic and/or maternal levels of toxic substances (or substances which may become noxious when above certain levels), such as antidepressant drugs or their metabolites, and dispenses substances to counteract the effects that such unwanted substances may have for the fetus.

[0025] Another aspect of the present invention provides a method of using a drug delivery system for decreasing the risk of premature labor or miscarriage, by sensing physiological and chemical changes delivering drugs to stop the process of premature labor or miscarriage (e.g., premature contractions), if either the physiological or chemical changes indicate that labor may be beginning prior to a desired time.

BRIEF DESCRIPTION OF THE FIGURES

[0026] These and other features of the preferred embodiments of the invention will become more apparent in the following detailed description in which reference is made to the appended drawings by way of example only, wherein:

[0027] **FIG. 1***a* shows an exemplary embodiment of a drug delivery device;

[0028] **FIG. 1***b* shows an alternative exemplary embodiment of the drug delivery device of **FIG. 1***a;*

[0029] **FIG. 1***c* shows an alternative exemplary embodiment of the drug delivery device of **FIG. 1***a;*

[0030] **FIG. 2** is a block diagram of a preferred embodiment of the control apparatus of **FIGS. 1***a*-**1***c;*

[0031] **FIG. 3***a* shows one embodiment of a drug pump implanted in a mother for drug delivery to the fetus; and

[0032] **FIG. 3***b* shows one embodiment of a method of using the drug pump to treat the fetus.

DETAILED DESCRIPTION

[0033] The systems and methods for modulating the fetal environment and pregnancy process can be used to treat a wide variety of medical conditions that affect the health and development of the fetus. In one embodiment, a medical drug delivery system (DDS) is used which is fairly complex, including sensors, active pumping elements, and one or more reservoirs. However, the some of the described treatment methods may be accomplished by using a constant flow pump powered by gas or a spring, an osmotic flow pump, a microchip drug delivery device, nano-particle drug delivery, or even a drug eluting stent. The properties of the DDS which are needed for the particular drug treatment can determine the type of DDS which is used. Accordingly, in the current specification, several DDS embodiments are described which can be used to accomplish the methods modulating the environment of the fetus. The DDS can be completely implanted, may be primarily external, or may be a combination of the two, for example, it may be realized by implanted sensors and catheters which lead to a base unit worn on the belt of the implantee.

[0034] The medical drug delivery system (DDS) is part of a system that dispenses drugs into any region of a pregnant implantee (or a female implantee slightly prior to fertilization), including areas related to reproduction and their supporting vasculature. The terms “drug”, “medication”, “active agent”, or “fluid” can all be used to mean a therapeutic agent delivered with the goal of producing a desired effect. The drug may often be stored within the DDS in the form of a fluid or gel, however, the DDS can also contain powder forms of drugs which are mixed with, dissolved or suspended within fluids prior dispensing them to an implantee. The types of fluids which can be delivered by the DDS

include, but are not limited to, medications, vitamins, nutrients, chemicals, antibiotics, hormones or hormonal drugs, catalysts, gene/germ therapies, anticoagulants, chemotherapeutics, antigens, anti-tumor agents, analgesic, anti-inflammatory agents, antioxidants, parasiticides, and others. Other drugs which can be delivered are listed in prior art (e.g., U.S. Pat. Nos. 5,980,508, 6,571,125 & US 2003/0093063 A1, & US2003/0130645 A1, which are incorporated by reference herein). The DDS can deliver fluids that contain nanoparticles or that activate drugs or nanoparticles (termed "catalysts"), and/or cause the membranes of the nanoparticles to disintegrate and release drugs. The DDS can also emit light or energy at a particular frequency (e.g., via a non-thermal laser) which may be located the tip of a catheter in order to activate, for example, photosensitive drugs/nanoparticles that are contained within the fluids it releases to various targets (e.g., porfimer sodium, Photofrin, Verteporfin). Nanoparticles (and the similar "microemulsions" and microfabricated particles) can contain substances such as medications, and can, for example, be introduced into the body to move along in the bloodstream toward their targets, or can be delivered locally. For example, a drug delivery system may be comprised of an apparatus that activates nanoparticles when they reach the fetal or placental compartment, so that the intended drug is primarily delivered to the fetus, although the drug is supplied at a distal site.

[0035] The types of medical conditions that the drug delivery systems and methods might be used to treat include, but are not limited to disorders of the pregnant mother and/or fetus involving, cardiovascular abnormalities and diseases, arthritis, pain disorders, disorders of the spine, neurological or psychiatric pathology, migraine disorders, infections, cancer, diabetes, systemic illnesses, biological and metabolic abnormalities requiring treatment. The drug delivery systems and methods can be used in medical, contraceptive, gynecological, pharmaceutical, veterinary, and research applications. Additionally, the a drug delivery system can be implanted in a mother and instead of, or in addition to, delivering drugs to the mother, can deliver drugs directly to a developing fetus, into the umbilical cord, or to an area near the fetus (e.g. the amniotic fluid) in order to provide drug to the fetus or in order to effect a therapeutic change in that area.

[0036] Terminology used herein is for illustration and convenience only and is not to be taken as a limitation of the invention. Words such as "upper", "lower", or "downward" can be used to describe embodiments shown in the figures. However, the components of the DDS can be oriented and configured in many directions and the terminology should be understood as encompassing such variations unless specified otherwise. More specifically, "upstream" or "proximal" refer to a point in the fluid path that is closer to reservoirs while "downstream" or "distal" refer to a point in the flow pathway which is operationally closer to point at which the fluid will be delivered to the implantee. Operating components in a "forward" direction causes fluid to move distally while causing fluid to travel in a "reverse" direction signifies moving fluid upstream towards the reservoirs. Further the illustrations are not drawn to scale, and the various components can be different shapes and sizes as long as the function does not deviate from the structures illustrated in the figures. For example, the width (i.e., internal circumference) of the lumens of the catheters may be much smaller than those which are shown here, or may vary in their width at different points (e.g., at their distal tips), but in order to illustrate internal components of the catheters, the catheters were shown with large internal widths.

[0037] Turning to **FIG. 1***a*, an implantable DDS **10** is shown. In this exemplary embodiment, the internal components of the system **10** are enclosed in an implantable housing **12** which may be made of titanium with a plastic outer coating. Within the housing **12**, is located fluid containment means which is realized in **FIG. 1***a* by a first reservoir **14***a* and second reservoir **14***b*, which are connected to a catheter hub **16** or output port. The catheter hub **16** allows a catheter to be attached to the DDS. For example, catheters can be slipped over, or screwed onto, the hubs, or the DDS can be manufactured with the catheters glued to or formed upon the catheter hubs. In this specification, a catheter refers to a single lumen through which fluid may travel. In the case of a multiple lumen catheter, each lumen can be connected to a separate catheter hub. The first reservoir **14***a* is connected to the catheter hub **16** by a fluid channel **18***a*, which in this example, is realized by a connection tube. The fluid channel **18***a* allows fluid to travel from the first reservoir **14***a* to the catheter hub **16** or to an intervening internal component such as a mixing chamber which it enters prior to arriving at the catheter hub **16** and fluid channel **18***a* may be formed as part of the reservoir **14***a*. The second reservoir **14***b* is also connected to the catheter hub **16** by fluid channel **18***b*, which in this case is also a connection tube. The first and second reservoirs **14***a-b* can also be referred to as "Res**1**" and "Res**2**", respectively. Flow from Res**114***a* through the fluid channel **18***b* to the catheter hub **16** is controlled by the control apparatus (labeled as "CA" in the figures and also referred to as a flow control module) **22** which controls flow by operating one or more pumps to cause fluid to flow and also manipulating the state of flow controllers (e.g., **20***a-b*) to control the path through which this fluid may travel. For example, the control apparatus can deliver fluid from Res**114***a* by operating a pump **23** so that fluid is pushed out of Res**114***a* and changing the state of flow controller **20***a* for the Res**114***a* in order to control the flow of fluid, which in this case entails permitting fluid to flow from Res**114***a* to the catheter hub **16**. The flow controller **20***b* for Res**214***b* is also shown.

[0038] Sensors such as the sensor **21** can be placed in the catheter hub **16** and can measure the rates at which fluids travel, or "flow rate" and send this information to the control apparatus **22**. The term "sensor" can refer to a sensor placed anywhere, either within or outside of the DDS housing, which provides sensed data relating to physical, chemical, physiological or other measurements relating to DDS operation, drug delivery, or the implantee or fetus. Sensors of the DDS can also include electrical (e.g., to measure the amount of residual charge in power supply, current flow, or impedance), chemical, optical, thermal, flow, volume, position, pressure, gas, oxygen, and biosensors or other types of sensors. A sensor may provide sensed data relating to multiple characteristics, for example, the flow rate, concentration, and pressure of a fluid which is being delivered by the DDS. Accordingly, a sensor may be an aggregate of several types of specialized structures each configured to sense a different fluid characteristic of the environment in which it is located.

[0039] The sensors utilized by the DDS can also include, but are not limited to, electrical (e.g., EKG electrode),

chemical (e.g., pH), electrochemical sensors (e.g., microelectrode arrays made by Quanteon for measuring substances such as glutamate), or optical sensors (e.g., which can detect O2, C02, and PH levels, and which can take the form of pulse oximeters or chromophore-based IO biosensors having one or more sensing fibers), and can detect physical measures (e.g., pressure, temperature, flow, acceleration), enzymatic changes, or the state of tissue or an organ. The sensors can be biosensors which are capable of sensing one or more specific molecules or other biological substances, either directly or by means of their metabolites. As is known to those in the art, sensor technology is continually advancing, however, some types of sensors which may be used are now described. The sensors can be similar to, based upon, or incorporate, nanotechnology such as Nanogen's NanoChip® Electronic Microarray, which uses a tiny, silicon chip that is capable of rapid identification and precise analysis of biological molecules. Additionally, an interaction between molecules may also be identified by using real-time BIA (Biomolecular Interaction Analysis, Pharmacia Biosensor AB) which detects surface plasmon resonance (SPR), an optical phenomenon. U.S. Pat. No. 5,791,344 to Schulman et al. entitled "Patient Monitoring System," proposes a system to monitor the concentration of a substance in a subject's blood wherein one enzymatic sensor is inserted into a patient to monitor glucose. Similarly, EP1011797 to Schulman et al, entitled "System of Implantable Devices for Monitoring or Affecting Body Parameters," proposes using microsensors to measure, for example, glucose level, oxygen content, temperature, and other measures. There are also a number of implantable medical devices and systems which monitor physiological data associated with the heart via telemetry (e.g., U.S. Pat. No. 5,720,771 to Snell entitled, "Method and Apparatus for Monitoring Physiological Data From an Implantable Medical Device"). Additionally, US application 20030171711, entitled "Closed-loop drug delivery system" employs a chromophore-based IO biosensor having one or more sensing fibers implanted directly into patient tissue. The contents of these prior art examples are hereby incorporated by reference as if recited in full herein. When possible, the DDS can rely upon completely implanted sensors, but may also communicate with, external devices, or may utilize information derived from assays, or laboratory techniques, in order to obtain accurate sensed data of the desired measures.

[0040] The term "flow controller" can refer to one or more valves (e.g., a piston, umbrella, disc, poppet, duckbill, ball, flapper, shuttle, gate, or other type of mechanism which functions as a valve to halt or redirect flow) which have at least one "open" state where fluid may pass, and a "closed" state where fluid may not pass. The flow controller, generically referenced as reference numeral **20**, can use more than one type of valve or mechanism to control flow within, into, and out of the DDS and its catheters. The flow controller can also incorporate a pump to actuate a direction and/or magnitude of the fluid flow within, into, and out of the DDS. Accordingly, the term "flow controller" can include one or more valves and/or pumps. In an "open" state the flow controller may use several valves some of which are open and some of which are closed to direct fluid along a specific path, and accordingly the "open" state refers to whether a particular fluid path is "open", allowing fluid to pass or "closed", inhibiting fluid from passing. The flow controller can take the form of a "hub" structure which receives fluid from at least one source at its proximal port(s) and direct this fluid to one or more target paths through its distal ports. The number of proximal ports can be less than, equal to, or greater than the number of distal ports.

[0041] The flow controllers of the DDS can be realized using different types of mechanisms which are described in the prior art and which are currently used in implantable pump devices. For example, US 2002/0193751 A1, incorporated herein by reference, discloses flow controllers, such as flow diverter or flow regulator based upon one of the following: a rod element, a pump, a solenoid, or a rotatable valve, which may or may not have a diversion conduit, a deformable conduit which may be squeezed shut by gas or hydraulic, pressure. U.S. Pat. No. 5,643,247, incorporated by reference herein, includes microparticle switching devices for stopping or redirecting flow, or for use as mechanical actuators or minipumps, and which can be used in the DDS, including the catheters (e.g., at either proximal and distal ends, and, for example, to accomplish inter-lumen flow control or circulation of a fluid circuit). The plurality of flow controllers **20** for the DDS is referred to collectively as a flow control system operated by the flow control module **22** as described herein.

[0042] The states of the flow controllers **20***a*, **20***b* can be determined by the control apparatus **22** or flow control module. The states of the flow controllers enable the DDS to route fluids within its internal components. For example, flow controllers **20***a,b* are operated by the control apparatus **22** to control the flow of fluids so that these may travel from each reservoir **14***a,b* to a specific catheter hub **16***a*. Flow controllers (e.g. **20***r*) also allow for the control of fluid flow during filling and refilling operations. Any set of mechanisms which enable the flow of fluid to be controlled so that it is encouraged or inhibited from flowing along one or more fluid paths is understood to be a fluid "flow controller". In the embodiment shown in **FIG. 1***a* the fluid flow controller is realized by the control apparatus and the flow controllers whose states it determines in order to direct the flow of fluids along the different fluid channels of the drug delivery device DDS.

[0043] The DDS is filled in order to provide the fluid for subsequent drug delivery. At least one replenishment mechanism is incorporated into the DDS which serves to securely join with an external fluid source connector so that the DDS can be filled with fluids. In **FIG. 1***a*, a replenishment mechanism is shown which is comprised of an inlet/input port **24** which resides in the housing **12**, and which includes a re-sealable port **26** or "septum", which is designed to make a secure connection with an external fluid source connector (e.g., the septum may be punctured by catheter which terminates with a syringe). The inlet port **24** allows fluid to travel through the inlet port fluid channel **18***r*, when permitted by a flow controller **20***r* for regulating flow of fluid from the inlet port to internal components of the DDS (e.g. reservoirs **14***a,b*, channels **18***a,b,r*). In **FIG. 1***a* the inlet port fluid channel **18***r* allows fluid to travel from the inlet port **24** to the catheter hub **16**, although, alternatively, the port **24** can be connected by inlet port fluid channels **18***r*,**18***r'* directly to one or more of the reservoirs **14***a,b* (e.g. see **FIG. 1***b*) or to other internal components of the DDS. Additionally, several inlet ports **24***a,b*, inlet port fluid channels **18***r*,**18***s*, and flow controllers **20***r,s* can allow for different fluids, that are dispensed through an external fluid source

connector coupled between the fluid source and at least one of the inlet ports **24***a,b*, to be routed to different components of the DDS (e.g. see **FIG. 1C**). Further the DDS can have one type of replenishment mechanism that is configured for refilling the DDS prior to implantation, and another replenishment mechanism that is configured for refilling the DDS once it is implanted.

[0044] At least one non-leaking reservoir (e.g. **14***a*) holds fluid that will be dispensed by the DDS. The reservoirs can be embodied in many ways. For example, each of the reservoirs can be lined with a balloon made from an elastic material and can utilize a plunger that collapses against one side of the balloon, in order to create a positive pressure that forces fluid to be dispensed, as is taught in the U.S. Ser. No. 10/099,060 patent application (the '060 application), incorporated by reference herein. At least one reservoir pump **23** (see **FIG. 2**) which is controlled by the control apparatus **22**, can modify the positions of the plungers in order to control flow from one or more reservoirs. Alternatively, the reservoirs **14***a-b* can be realized using a dual chamber reservoir wherein a first chamber contains the infusate and another is pressurized with a gas or fluid which causes the infusate into or out of the first chamber under the control of the control apparatus **22**, which utilizes the positive/negative pressure of the gas or fluid as pumps **23** for at least one reservoir. Other embodiments of the fluid containment means are also possible.

[0045] The pumps **23** for at least one reservoir **14***a*, as well as the other pumps of the DDS and its catheters, can be realized using a stepper motor, lead screw and anchored lead nut, as is taught in the '060 application. Additionally, the pumps can be realized through a piston, diaphragm, bellows, screw or other type of pump and can operate via hydraulic means, spring means, stored pressure, and many other means as are described in the prior art. The pumps **23** may be, for example, mechanical (e.g., spring powered or gas powered), electro-mechanical (e.g. screw type, hydraulic, piston, worm gear, peristaltic or displacement mechanisms, or pulley mechanism as described by, for example, U.S. Pat. No. 6,394,981, the "981" patent), or osmotic, where a valve under control of the control apparatus **22** may determine how much liquid is exposed to a swellable agent in order to adjust the amount of pressure imposed on a drug by the pump. The DDS may contain more than one type of pump **23** and more than one type of reservoir. Additionally, rather than having a separate pump **23** for each reservoir, one pump **23** can be used to accomplish the pumping operations for one or more reservoirs, for example, using a gear assembly. Although in **FIG. 1***a* various components of the DDS (e.g., the reservoirs, pumps **23**, or rechargeable power supply) are located inside the DDS housing **12**, these can also be distributed so that some components are situated in separate locations that are easily accessed and that are external to the housing, as is described in U.S. Pat. No. 4,588,394, which is incorporated by reference herein. U.S. Pat. No. 6,551,235, incorporated by reference herein, shows an alternative to gear pumps, wherein a valveless pump consisting of a magnetically manipulated cylinder is used to pump fluid. Such a pump could be incorporated into the connection means and could be used to draw fluid from the reservoirs rather than, or in addition to, having the pumping means **23** exerting a positive pressure on the reservoirs. Valves which could be used in the pump are made by Lee Company, Westport, Conn. and can be, for example, a solenoid valve, latching solenoid valve, IMH orifice for liquids, or a VHS micro-dispense valve. Accordingly, it is recognized that pumps **23** and assorted valves of the flow control system are collectively referred to as flow controllers **20**.

[0046] The control apparatus **22** controls the components of the DDS to achieve controlled flow of fluids used during drug delivery, for example, by independently activating the pumps **23** to cause increased or decreased pressure to be produced within any reservoir contained in the DDS and controlling fluid flow along specified paths. The control apparatus **22** can either communicate with pumps or, as occurs in many of the embodiments illustrated in the FIGs of this application, can contain the pumps for the reservoirs. The control apparatus **22** contains hardware/circuitry (which may run according to a software program) that allows the control apparatus **22** to control drug delivery, operate the DDS in its various modes, sense changes in the implantee, and achieve many of the other operations described herein. Alternatively, some of the functionality achieved by the components of **FIG. 2** can be realized in the form of software which is executed by the processor **304**. The control apparatus **22** also provides power to/controls/communicates with/pumps, sensors, and flow controls of the catheters. While the electrical wires and connections are not shown in the figures, to prevent cluttering of the figures, it is understood that electrical/hydraulic connection, which may be in the form of a wire/tube harness, connects the control apparatus **22** (and/or the power supply) to each of the components (e.g., pumps, sensors, flow controllers **20**) that it controls in the DDS and its catheters.

[0047] A preferred embodiment of the control apparatus **22** of FIGS. **1**A-C is shown in **FIG. 2**. The control apparatus **22** includes sufficient computer hardware **300** for accomplishing its tasks. As is well known in the art, the computer hardware **300** includes, for example, components such as a processor **304** with a real-time clock, memory **308** (e.g., EEPROM, RAM, flash) for storing information such as delivery protocols or DDS events (e.g., activity, flow rates, sensor levels, etc.). The computer hardware **300** of control apparatus **22** includes, or is in functional contact with, a power supply **312**, such as a rechargeable battery which provides the power needed to run the DDS. The computer hardware can also contain custom circuitry **316** which contains, for example, alarm circuitry which triggers an alarm when the software program **320** determines the DDS is malfunctioning. The software program **320** can exist in the memory **308** and can be loaded, modified and updated by the implantee, manufacturer, or medical personnel. The software program **320** enables the computer hardware **300** to perform all DDS operations and contains software subroutines or "modules". For example, modules of the software program **320** can include a database module **320***a* which includes a database **322** and associated routines for retrieving/storing/querying information in the database, a statistics module **320***b* for performing univariate and multivariate statistics upon data, or transforming the data into factor or discriminant scores (as has been previously described by the inventor in U.S. Pat. No. 6,066,163, and its related applications, incorporated by reference herein), a modeling module **320***c* for performing pharmacokinetic modeling, which can be based upon sensed data, or for performing modeling of pumping operations (e.g. in order to determine how the DDS operates to dispense a drug along a certain fluid path while taking into consideration the amounts and types of

fluid already stored in that path). The modeling module **320***c* enables the software program **320** to run simulations of the DDS in order to accurately determine the drug delivery which will occur when the DDS components are operated according to a specific set of instructions and enables the creation of accurate, mathematical models of how fluid will flow within the physical drug delivery system.

[0048] The digital signal processing (DSP) module **320***d* contains DSP routines for performing, for example, filtering, frequency analysis, and many other DSP routines as is known in the art. The evaluation routines module **320***e* contains routines for determining if a positive result has occurred, in which case drug will be dispensed according to a drug delivery regimen, or negative result has occurred, in which case no drug will be delivered. The evaluation routines module **320***e* can contain algorithms for evaluating the sensed data, such as, pattern recognition and template matching routines, and algorithms related to performing evaluation of, for example, whether sensed data meet, or fail to meet, threshold criteria or statistical criteria which can be univariate or multivariate. When the DDS contains electrical leads for providing electrical stimulation instead of, or in addition to, pharmacological stimulation the positive and negative results of the evaluation routines module **320***e* will similarly determine if electrical stimulation occurs. It is obvious that the software program **320** can contain additional software modules, or alternatively, may contain fewer modules and instead these modules can be either accomplished by analogous hardware, or can be located in the external patient controller which may execute its software routines much more quickly and without using power of the implanted DDS.

[0049] The computer hardware **300** of the control apparatus communicates with, and provides power to, the programmable input/output data acquisition hardware **328** (DAQ) via its multiplexor/bus hardware **324**. The DAQ **328** contains circuitry which permits the control apparatus **22** to control, communicate, and/or provide power to all the other components of the DDS, its catheters, and external components such as remote sensors, the external patient controller, and other components which may or may not be in direct physical contact with the DDS, but which can be used with the DDS to assist in drug delivery. The DAQ **328** contains amplifier circuitry **332** for amplifying data sensed at external sensors, for example, EMG activity. These signals can then be passed through signal processing/filtering circuitry **336** which may consist of hardware that is able to provide rapid or real-time signal processing and filtering of the sensed data. Additionally, some sensors may contain amplifying/filtering/signal processing circuitry within them and the components of the DAQ can act as a second stage of amplifying/processing or the sensors can communicate directly with input/communication channels of the DAQ hardware. Accordingly, the DAQ **328** also contains communications/power/telemetry hardware **340**, for communicating with and providing power to the components of the DDS. For example, the control apparatus **22**, can communicate with the external patient controller or external instrumentation that monitors information that is relevant to the drug therapy (e.g., a patient's heart rate), or with sensors which may be coupled to the catheters either through a direct physical link or through telemetry. The communications/power/telemetry hardware **340** can also allow for controlling and/or sensing the internal operations (e.g., pump movements), levels (e.g., fluid levels in reservoirs), and states (e.g., flow control states, pressure levels or flow rates) during DDS operation. The communications/power/telemetry hardware **340** can also connect to an electrical harness (although this is not shown in the figures to prevent cluttering of the figures) which provides an electrical/communication connection from the CA **22** to all other components of the DDS, and it should be understood that such a harness allows the DDS embodiments shown in, for example, **FIGS. 1-3**, to operate.

[0050] The control/sense circuitry **344** of the communications/power/telemetry hardware **340** also contains circuitry for controlling the states of the flow controllers of the catheters. The communications/power/telemetry hardware **340** further contains specialized control/sensing circuitry **344** which can contain multiplexors, communication hardware, and specialized control, processing, and sensing circuitry for controlling components and sensing information during pump operation. The control/sensing circuitry **344** which is configured to communicate with (e.g., receive information sent by, or send power and control commands to) sensors of the DDS. The control/sensing circuitry **344** contains pump control/sensing circuitry for achieving pumping operations, filter control/sensing circuitry for achieving filtering operations, pulse generator/sensing circuitry for stimulating electrical leads or sensing information from these leads, flow control/sensing circuitry for achieving flow control/sensing of the fluids during drug delivery operations, and power control/sensing circuitry for modulating and monitoring power usage related to the power supply **312**. The control/sensing circuitry **344** may also have dedicated circuitry for processing data, for example, data that are sensed by external sensors located outside of the DDS housing **12** which may only be sent to the computer means when a specified condition is met. The control/sensing circuitry **344** can control/receive information from external sensors which can sense physiological, chemical, EKG, EEG, and other signals. In some embodiments, the external sensors are connected to the control apparatus via an external sensor/stimulator connection port **28** (e.g., see **FIG. 1***a*). When the sensors are electrical, such as in the case of EEG, the control apparatus can also send stimulation signals out of external sensor/stimulator connection port **28** to the electrical sensor/stimulation lead.

[0051] The control apparatus **22** can activate the internal components of the DDS in a specified manner to achieve desired drug delivery. In the embodiment of the control apparatus **22** shown in **FIG. 2**, controlled delivery is made possible, in part, by the database software module **320***a* of the software program **320** of the control apparatus **22**, which includes a database **322** having one or more tables containing information, termed "data". For example, the database can contain state tables ("Sts") which indicate current DDS characteristics, such as pump states St**1** (e.g., positions) and flow control states (e.g., "open", "closed", or which of several "open states" is currently set to allow for various flow paths). A table of flow control states St**2** provides the DDS to switch between different pumping modes and operations and permits the pump DDS to operate efficiently. For example, if a mode requires that a flow control be set to its open state and it is already in that state then time and energy are not wasted sending an additional command for the flow control to change to an open state. Additionally, the software program **320** can use the flow control state table St**2** to

monitor that the flow controls (e.g. **20***a*) are in the correct states and are not malfunctioning or blocked. The state tables can also include pressure/power/temperature/flow state tables St**3**. For example, the pressure level tables can include intra-catheter pressure levels and pressure levels which exist outside of the DDS, in the implantee, and can be used in order to adjust pumping operations so that fluids are dispensed as intended by the drug delivery regimen. Further, the software program **320** loaded into the memory **308** and implemented by the processor **304** of the computer hardware **300** of the control apparatus **22** can periodically check the pressure/power/temperature/flow state tables St**3** of database software module **320***a* to provide that the power supply **312** contains at least a specified amount of charge, and if not the processor **304** can send an alarm signal through the multiplexor/bus **324**, to the communication/power/telemetry hardware **340** which transmits this signal to an external patient controller and warns the implantee that the DDS must be recharged. The state tables can also include a fluid volume table St**4** which contains updated information about the amounts, concentrations, and types of fluids contained in the different reservoirs, catheters, catheter fluid circuits, and other components of the DDS.

[**0052**] The state tables can also include sensed data table St**5** which can contain information such as the current concentration of a particular drug in a mixing chamber, pressures and flow rates at the distal tip of the catheter or along the catheter, or the current estimate of the muscular tremor of an implantee which has been obtained by having the processor **304** use the digital signal processing software **320***d* to analyze a digital representation of sensed data is provided by the control/sense circuitry of the communication/power/telemetry hardware **340** of the DAQ board **328** after an EMG signal sensed by an EMG sensor has been amplified and filtered by amplifier hardware **332** and filter hardware **336**. The information contained in the sensed data table can include tables related to self- or population norms for the mether, and for the fetus, both of which may be used to evaluate the sensed data. Other types of state tables can be included as well.

[**0053**] The database **322** can also contain a plurality of reference tables ("Rts") which hold reference information that is relevant to achieving a desired drug delivery or information related to past pump activity, information such as delivery routines and protocols used to deliver a particular treatment regimen, number of hours of use, current estimated gestational age of the fetus, the amount of drug delivered between various dates, average power consumption, and other types of reference information. A historical data reference table Rt**1** can include, for example, a record of all past sensed data for both the mother and the fetus, a partial record of past sensed data, statistical summaries of the characteristics of past sensed data, and a record of pump events. Pump events can include general records of delivering drugs, their amounts and the times of delivery, and specific records which can include all DDS operations such as activating a pump or opening a flow control. A lengths and volumes reference table Rt**2** can contain information about the physical dimensions of various DDS components, such as the lengths and volumes of the catheters which were implanted in the implantee. A population/self normative values table Rt**3** can contain population norms appropriate for the age/sex/weight of the implantee and/or of the fetus. This table can contain normative values for sensed information that is, for example, sensed by external sensors (or sensed by external instrumentation and sent, via telemetry to the DDS) such as tissue state, pressure levels, concentration levels of drugs, metabolites, and chemicals present in the implantee (or fetal environment) which can further be qualified in terms levels which existed at specific times before, after, or during prior deliveries. This table can also contain normative values for subjective measures inputted by an implantee using an external controller. A delivery routines/protocols table Rt**4** can contain information related to dispensing drugs according to different treatment regimens. A model values table Rt**5** contains information related to pharmacokinetic modeling of the implantee. Models can be based upon normative values or can incorporate values sensed by the sensors of the DDS. A patient/pump reference table Rt**6** can contain information about the bodyweight and age of the implantee, and information about the DDS such as serial numbers of components, DDS identification numbers, software program ID and version number, the viscosities and types of fluids contained in the DDS. Other types of reference tables can be included as well. The values in the database **322** can be accessed or updated by the software program **320**, loaded into the memory **308** of the computer means **320**. The database module **320***a* and the database **322** can also be realized partially or completely in hardware rather than software form. An illustrative example of how the control apparatus **22** may perform drug delivery by using the database is as follows:

[**0054**] the software program **320** uses the database module **320***a* to check the delivery routines/protocols table Rt**4** of the database **322** and determines that sensing is to occur at a particular sensor

[**0055**] Sensing causes the sensed data to be updated in the sensed data table St**5**

[**0056**] according to the evaluation routines module **320***e* which compares the sensed data to a self normative value contained in the population/self normative values table Rt**5**, via the statistics module **320***b*, a positive result has occurred and drug must be dispensed

[**0057**] the software program **320** determines that a particular drug at a particular concentration must be delivered from a specific catheter hub **16***a*, refers to the fluid volume table St**4** and determines both that the fluid to be delivered is in Res**114***a* and also that there is only buffer fluid in the catheter attached to that hub **16***a*, and then refers to the lengths and volumes table Rt**2** to determine how much fluid must be dispensed in order for a desired amount of drug to be dispensed from the tip of the catheter

[**0058**] the software program **320** then operates the computer hardware **300** to cause the necessary flow controllers **20***a*, **20***b* to be set to the correct states (e.g., **20***a* set to open state, **20***b* set to closed state) and operates the pump **23** for Res**1** in order to cause the fluid to be delivered to the implantee.

[**0059**] As reflected in this example, in order to deliver a drug out of a specific catheter the DDS the software program **320** of the control apparatus **22** can use information held in its database **322** in order to provide appropriate control operations for its internal components. The software program **320** and information contained in its database **322** is used to control the flow of fluid in the DDS by manipulating

the internal components of the DDS, such as by changing the state of the flow controllers **20** as different pumps are activated, and thereby permitting fluids to be dispensed from one or more reservoirs to one or more catheters at specified concentrations and rates.

[**0060**] The communication/power/telemetry hardware **340** of the control apparatus **22** allows the DDS to communicate with external instrumentation that is often used in conjunction with implanted devices, such as a specialized computer or an external patient controller. The communication/power/telemetry hardware **340** can contain an alarm warning which can activate an auditory, visual, or vibratory warning (in the DDS or the external controller), and can transmit a signal through the internet or phone or over a wireless connection (e.g. via the external controller). The communication/power/telemetry hardware **340** facilitates the external instrumentation to modify the DDS operation and drug treatment (e.g., allows for patients or medical personal to program the DDS or allows for patients to administer or change a dose) and facilitates other operations which respond to patient commands, allows setting of routines and regimens of drug administration, and allows the DDS to deliver drugs in response to sensed data, for example, to create closed-loop drug delivery. The communication/power/telemetry hardware **340** also facilitates data to be sent to the external instrumentation which can perform operations such as signal processing on such data. Such data may be, for example, biological, chemical, physiological measures recorded from the patient, or summaries, statistics, transformations of these measures such as PCA factors or discriminant scores.

[**0061**] The control apparatus **22** works according to data relevant for different drug delivery regimens which are stored in the delivery routines/protocols tables Rt**4** of its database **322** of the DDS, and which may cause predetermined amounts of fluids to be dispensed at specified rates, for predetermined amount of times, and in pre-determined patterns (e.g., a continuous rate, large bolus, small bolus, repeated small bolus doses delivered in a rapid or slow manner, etc.). For example, U.S. Pat. No. 6,475,180 (the '180 patent), describes several delivery modes, such as a basal rate delivery which also allows for patient controlled delivery to be periodically superimposed, repeatable constant doses, constant rate, allows for switching from one mode to another, and describes a drug pump which can perform internal self tests and calibration operations. Further the '180 patent describes an external patient controller which can communicate with external instrumentation and measurement means that can include temperature sensors, blood pressure sensor, EKG monitor, or EEG monitor.

[**0062**] The drug delivery device DDS of **FIG. 1***a* delivers drugs in response to the sensed data. Sensors can be located both internal to and external to the DDS's housing **12**. Internal sensors can include, for example, power sensors for the rechargeable battery, air/gas detectors, pressure, level, and temperature sensors, motor position sensors. External sensors can sense concentrations and chemicals which exist in external fluids that are located in different areas of the body of the implantee and in the fetal environment, as well as temperature, physiological processes such as EKG/EEG, etc for both the mother and the fetus. Data, sensed by these sensors can be analyzed by the computer **300** of the DDS or can be sent to the external patient controller for analysis. The patient can also input subjective experiences such as being nauseous.

[**0063**] The DDS can provide an external patient controller with DDS component information about how much drug is left, can provide a log of usage (e.g., a rate of use calculated as a percentage of total drug at start) and related information such as amount of power used to accomplish various types of drug delivery, amount of pressure required to deliver drug, etc, and can issue warnings to the user, which alert the user to problems or potential future problems which may occur, such as lack of power or drug. For example, the control apparatus **22** can sense data from pressure detectors, which can serve to function as occlusion detectors, which detect when flow is blocked, for example when a dedicated circuit determines pressure is above a specified threshold level. The DDS can automatically modify, or allow the patient to modify via the external patient controller, a previous delivery regimen based upon recent trends in the history of the implantee.

[**0064**] The control apparatus **22** of the DDS controls all operations of the DDS that are required during operation and maintenance. For example, due to the software program **320** that has been uploaded into the computer hardware **300**, the processor checks the real-time clock and determines that a specified amount of time has elapsed since the last sensing operation occurred. For example, the processor **304** reads the measurement of a chemical sensor which senses glucose level and determines that the reading is above a pre-specified level. According to the software **320**, the control apparatus **22** causes a specified amount of insulin to be dispensed by activating the pumping means for Res**114***a* while setting the flow controller **20***a* for Res**114***a* into an open state. The movement of the pump **23** causes a warning to be generated because data for the Res**114***a* kept in the fluid volume table St**4** indicates that the reservoir is diminished below a specified level. The telemetry circuitry of the control apparatus **22** sends a signal to an external controller indicating that Res **1** is low and will need to be replenished.

[**0065**] The embodiments shown in **FIGS. 1***b*-**1***c* contain components which are very similar or identical to those shown in **FIG. 1***a*. Accordingly, the same reference numerals have been used for the corresponding components.

[**0066**] In the embodiment of the DDS **10** shown in **FIG. 1***b*, the DDS **10** includes many of the same components as in **FIG. 1***a*, but also permits fluid from the implantee's body to be drawn upon to refill a reservoir, in this case Res**214***b*. Accordingly, the Res**214***b* contains an inflow fluid channel which may consist of inflow catheter **30** which permits fluid to travel from outside the DDS housing into Res**214***b*. The inflow catheter **30** may have a filter **34** on its distal tip, which may be a semi-permeable membrane. Additionally, the inflow catheter is coupled to a filter **25** so that fluid in the inflow catheter **30** can flow into an input port of the filter **25** when flow control **20***k* is set to an open position which directs flow into the filter **25** (and does not permit flow to continue more proximally in the inflow catheter **30**) and out of an output port of the filter **25** and into Res **214***b* when flow control **20***n* is set to an open position. The filter **25** may have its own pump which is under control of the control apparatus **22** or can rely upon the pump **23** of Res**214***b* to cause fluid to flow through it. As will be described, the filter **25** can rely

upon physical, chemical, or other modes of filtering to filter fluids drawn into the DDS. The proximal tip of the inflow catheter **30** has an inflow flow controller **32** which is under the control of the control apparatus **22**. When operating the DDS according to some of the delivery regimens, the states of the flow controllers **20***b*, **32** are set so that fluid drawn into the DDS is routed out to the catheter hub **16** rather than back out of the inflow catheter **30**. For example, the inflow flow controller **32** is set to a closed position, which does not permit fluid to pass, while the flow controller **20***b* for Res**214***b* is set in an open position which allows fluid to flow into the catheter hub **16**. The pump **23** for the reservoir is then operated in a forward position which causes fluid to leave the reservoir, travel through the catheter connection means and reach the catheter hub **16**. Drugs from other reservoirs can be mixed with this fluid in the catheter hub **16**. When the DDS is operated in one embodiment of the "implantee replenishment mode" fluid from the implantee is drawn into the inflow catheter **30** and then used to dispense drug. For example, the following steps could occur. The inflow flow controller **32** is set in an open position, which permits fluid to pass, while the flow controller **20***b* for the Res**214***b* is set in a closed position which does not allow fluid to pass. The pump **23** for Res**214***b* is then operated in a reverse direction (to create a "negative/suction pressure" or "vacuum") which causes a human fluid, for example, amniotic fluid, to enter the Res**214***b* from an external source, for example, the amniotic sac. Instead of being functionally connected to a reservoir, e.g., Res**214***b*, in an alternative embodiment (not shown) the inflow catheter **30** can simply be connected to the catheter hub **16** by a fluid channel which has a pump and which may also have at least one flow controller in order to route fluids from the implantee directly into the catheter hub. The DDS of **FIG. 1***b*, is also different from **FIG. 1***a*, in that it contains an inlet port **24** which is connected to Res**1** and Res**2** by inlet port fluid channels **18***r* and **18***r'* respectively, which use flow controllers **20***r* and **20***r'*.

[**0067**] In the embodiment shown in **FIG. 1***b*, the fluid channel **18***a* for Res**114***a* terminates more distally within the catheter hub **16** than the fluid channel **18***b* of Res**214***b*, and a catheter hub division **36** containing a catheter hub flow controller **38** is located between the locations where the fluid channels **18***a* and **18***b* connect to the catheter hub **16**. In one method of performing the Sequential Bolus mode the drug from Res**114***a* is loaded first into the catheter hub **16** and then the fluid from Res**214***b* is used to push the drug through the length of the catheter to the target site of the patient.

[**0068**] The DDS can be used for diluting a drug kept within the pump or for delivering a small amount of drug to a distal target, or for inhibiting residual drug remaining in a catheter due to prior drug delivery, which occurs when sending different drugs from the same catheter.

[**0069**] In another embodiment of the DDS, two or more reservoirs **14***a,b* are able to provide different fluids to two or more catheter hubs **16** (output ports) by relying upon fluid channels and flow controllers **20** which are under control of the control apparatus **22**. In **FIG. 1***c*, the implantable DDS **10** includes many of the components of the system shown in **FIG. 1***a*, and in addition to a first catheter hub **16***a*, there is now a second catheter hub **16***b*. Although not shown, each of the catheter hubs can be functionally connected to one or more mixing chambers rather than being directly connected to the fluid channels. Also, although these are not shown, a catheter #**1** is understood to be connected to catheter hub **16***a*, a catheter #**2** is understood to be connected to catheter hub **16***b*, and so on. The fluid channels connect the reservoirs to the first and second catheter hubs **16***a,b* which, in this example, is achieved by connection tubes **18***a*, **18***b*, **18***c*, and **18***d*, where connection tube **18***c* connects the Res**114***a* to the second catheter hub **16***b*, and connection tube **18***b* connects the Res**214***b* to the first catheter hub **16***a*. The Res**214***b* is also connected to the catheter hub **16***b* by a fluid channel, which in this case is a connection tube **18***d*. Two inlet ports **24***a,b* are shown in this embodiment, each connected to a separate reservoir using different inlet port fluid channels **18***r,s* and flow controllers **20***r,s*.

[**0070**] If fluids are to be sent out of catheters **1** and **2**, then the pumps **23** must pump about twice as much fluid volume compared to when the fluid only is dispensed out of one of the catheters (assuming catheters have similar volume). Accordingly, the control apparatus **22** controls the pumps **23** of the reservoirs **14***a*, **14***b* to provide the fluid which is to be delivered, and modifies the state of the associated flow controls **20**, to deliver drugs from one or more catheters according to a drug regimen.

[**0071**] Operational Modes

[**0072**] The DDS may operate in several operational modes including, but not limited to, the following: a Continuous mode, a Bolus mode, a "Sequential Bolus" mode, a "Flow-Return" mode, a "Flow-circulation" mode, a "Replenishment" mode, an "Implantee Replenishment mode", a "Sample-Push" mode, a "Filter" mode, a "Purging" mode, and a "Shunt" mode.

[**0073**] The Continuous mode and Bolus mode are where drugs are dispensed continuously, or at specific times, respectively. The Bolus drug delivery may occur according to many strategies, such as at least one of the following: in response to sensed data, in response to user commands, according to a specific chronological time, and according to a drug regimen.

[**0074**] In Sequential Bolus mode, a drug bolus is pushed from the DDS through the catheter attached to the output port **16** by a buffer fluid. The buffer fluids can be for example, a drug, a fluid that enhances the effects of a drug or the metabolism of a drug (i.e., an adjuvant), a nutrient, or a neutral/inert fluid, and may be primarily or totally miscible or non-miscible. Preferably the buffer fluid is an inert fluid that is mostly non-miscible with respect to the drug(s), so that it does not dilute the drug(s). If the buffer fluid is non-miscible with respect to one or more drugs, then one of the other reservoirs can be filled with a diluent so that various concentrations of drugs can be created prior to bolus delivery. The Sequential Bolus mode allows the DDS to deliver one or more drugs, and/or different concentrations of a particular drug in an exact bolus manner through at least a single lumen of the catheter to help inhibit problems created by "residual fluid" which is in the catheter due to prior dispensing of a drug.

[**0075**] By using a Sequential Bolus mode, where the drug is pushed through the catheter by a buffer fluid, the problem of unused drug in the catheter is addressed. This problem of residual fluid can also be addressed using a Flow-Return mode. The Sequential Bolus mode, or other drug delivery

mode, can be operated in conjunction with a Flow-Return mode in order to provide for further advantage over the prior art. In the Flow-Return mode either a buffer fluid or a drug used during a previous drug delivery is drawn back into the DDS (e.g., back into the reservoir **14** from which it originally resided) in order to clear the catheter, and/or other areas of the drug delivery system DDS, from the residual fluid which was not dispensed during that previous delivery. Further, by using a Flow-Return mode, without the Sequential Bolus mode, the drug can be pumped out of the reservoir **14** until the required amount is delivered and then the remaining drug in the catheter is drawn into the reservoir **14** by operating the pump **23** and flow controllers **20** to cause the fluid to flow back into the designated reservoir **14**.

[**0076**] The implantable DDS can operate in a Replenishment mode. In the Replenishment mode, fluids from outside of the body of the implantee are used to fill the drug-delivery DDS so that these can serve as a drug, buffer fluid or diluent during treatment. When multiple reservoirs **14***a,b* are included, the external drugs are routed to the correct reservoir. By operating the internal components of the DDS (e.g., the flow controllers **20**) in a coordinated manner these external fluids can be guided into appropriate reservoirs **14***a,b*. For example, the medical personnel can use an external patient controller (not shown) operatively coupled to the DDS to send commands to the CA **22** which cause the fluids that he or she provides in the fluid source to be guided into the correct reservoirs **14**.

[**0077**] The internal pumps **23** of the DDS act in conjunction with, or communicate with, an external pump associated with the fluid source in order to refill the internal reservoir **14**. By having both the external and internal pumps work together, the vacuum produced in the reservoir **14** when the pump **23** is operated in a reverse manner can not draw in unwanted fluid which may, for example, slip in between a needle and the septum of the input port **24** of the DDS. Further, provided is refilling more than 1 reservoir with different drugs from the single inlet port **24**. For example, in one embodiment the DDS uses a method of refilling the reservoirs **14** wherein all the flow controllers **20** are set in their "closed" position, except for the flow controllers **20** which enable fluid to flow to a specific reservoir **14** and the pump **23** for that reservoir **14** is operated backwards to pull the substance into the specified reservoir **14**, and the vacuum is substantially equivalent to help to balance the positive pressure provided by the drug supply pump associated with the fluid source, thereby helping to decrease the risk of an influx of air or increased pressure.

[**0078**] The Implantee-Replenishment mode enables fluid from the implantee to be drawn into the DDS and subsequently used as a drug, buffer fluid and/or diluent. The Implantee-Replenishment mode normally will use an inflow catheter **30** of **FIG. 1***b*, whereby fluid is drawn into the DDS from the implantee and then used to deliver drugs through one of the catheter hubs **16**. Further, the inflow catheter **30** can draw in fluid which it filters using either a filter on its distal tip **34** (see **FIG. 1***b*), or a filter located anywhere along its length. The filters used to filter the fluid entering the inflow catheter **30** may be a physical, chemical, electrical, osmotic or other filter or combination of several filters. The implantee replenishment mode provides the fluids of the DDS to last a longer time as compared to current technology. By using the fluids available inside the implantee, a relatively endless supply of buffer and diluent fluids (and certain biological fluids that can act as therapeutic agents), as compared to current systems, can be used without the need for the DDS be refilled.

[**0079**] The Sample-Push, Filter, Purging, and Shunt modes, like the Implantee Replenishment mode, normally utilize fluids from the inflow catheter **30** (although any of the catheters can be used). When operating in a Sample-Push mode, fluids can be drawn into the DDS from the implantee and can then be routed through the catheter hub **16** to the attached catheter which transports the fluid to the distal location where these samples can be accessed by medical personnel. In other words, if a DDS uses, for example, 5 catheters, then one of these catheters can be used to send fluid where medical personnel can easily access it. The end of this specific catheter, termed the "sample-push catheter" may be fitted with a small fluid containment system (e.g., a receptacle) in order to hold this fluid prior to its access by medical personnel. In this way, samples of substances which are proximal to the sites of drug delivery can be easily obtained for comprehensive analysis, for example, using chromatography, DNA, RNA, protein, or chemical assays and other analysis techniques. When the DDS operates in a Filter mode it may draw in fluid through the attached catheter to the hub **16** and, after filtering it by means of physical, chemical, electrical, or other means, the filtered fluid may be redeployed by the DDS through the same lumen of the catheter or through an alternative path. The filtrate can be disposed of by operating the DDS in a Purging mode, which is a variant of the Sample-Push mode, so that filtrate does not accumulate past a specific level within the DDS. For example, when operating the DDS in a Filter mode, the fluid to be filtered may rely upon one or more filters such as an electrochemical filter, a nanotube filter (e.g., nanotube membranes can be used to cleanly separate small molecules on the basis of molecular size as described in Wirtz et al, 2002), a chemical filter, or other filter acts to remove filtrate from the fluid. In the next step, the filtered fluid is drawn into the reservoir **14***a,b*, such as Res **1** until a specified amount of fluid has been filtered or a certain amount of filtrate has been obtained. In the next step, a buffer fluid is used to push the filtrate out of catheter hub **16***b* and into the connected second catheter which acts to purge the filtrate from the DDS and into, for example, an area of the implantee where it will not be harmful or the systemic circulation. The Purge mode can also be used to send unwanted air or gas which has entered the DDS (due to, for example, a chemical reaction which occurred during mixing of drugs or due to gas that was present in implantee fluids that were drawn into the DDS) so that this does not interfere with pumping operations or become mixed in the catheters attached to the hub **16** with the fluids to be dispensed. In another embodiment of the Filter mode, the fluid which is drawn into the DDS undergoes a transformation. For example, a chemical can be mixed with the fluid to change its chemical nature (e.g., increase its PH level). Additionally, substances can be mixed with the fluid which is drawn in from the implantee in order to functionally neutralize an unwanted characteristic of the implantee fluid by, for example, causing certain molecules in the implantee fluid which has been drawn into the DDS to bind with a therapeutic drug that acts to competitively bind with (or break down or transform) those molecules. After this fluid has been altered or "functionally filtered" with respect to the

unwanted characteristic, it can be re-dispensed from the DDS through the same or different catheter attached to the hub **16**. Since some of these changes require time it is sometimes advantageous to treat the fluid of the implantee within the DDS rather than by delivering fluid outside the DDS into the fluids of the implantee. Further, the filtering operations can be guided by sensors which are incorporated into the filter. The filter for the DDS can be configured so that the filtrate or unwanted fluid can be purged from the DDS distally from the fetal environment.

[**0080**] When the DDS operates in a Shunt mode, it first operates its pump **23** to draw fluid into the DDS through the hub **16***a* and then pumps this fluid through another catheter attached to a hub (e.g., **16***b*) to, for example, shunt fluid from the body of the implantee or to redirect this fluid to another area within the body of the implantee. In the shunt mode, and other modes, the DDS does not have to actively pump fluid from the implantee into the DDS, but rather the fluid of the implantee can enter the catheter **80** (or inflow catheter) due to natural pressure which biases the fluid to leave an area of the body and enter the DDS (i.e. passive rather than active fluid flow actuation, where, for example, the DDS sets the flow controllers to their open state so that a fluid path serves as a conduit between two catheters).

[**0081**] When a surgeon chooses the length of the catheters which will be used with the drug delivery DDS, or modifies the length of the catheter so that it efficiently delivers drugs to a desired area of the patient, the lengths and volumes of the catheters are programmed into the Lengths and Volumes table Rt**2** of the DDS (see **FIG. 2**) which is stored in the memory **308** of the CA **22**, which is stored in the computer **300**. By utilizing both the volumes of the fluids in the catheters and the real-time volumes of the DDS components such as the mixing chamber, calculations are performed by the processor **300** which allow appropriate amounts of fluids to be pumped, thereby achieving desired drug delivery.

[**0082**] The medical drug delivery system, may be completely implanted or may exist partly outside of the body, as is sometimes done with insulin delivery systems, for example, the MiniMed Paradigm™, insulin product, pager-sized device typically worn on a belt, drug is delivered through a transcutaneous catheter. Accordingly, some parts may be mounted externally or implanted subcutaneously.

[**0083**] Various components of the medical drug delivery system can be miniaturized considerably compared to the embodiments shown in the FIGs. The scale of components in the FIGs are for illustration purposes and do not necessarily represent the sizes and scales of the components. For example, miniaturized embodiments of the connection means, reservoir flow controllers, pumping means, and other components of the implanted DDS, can be based upon technology such as that described in U.S. Pat. No. 6,408,878, which is incorporated by reference herein, and which describes microfabricated elastomeric valves which may be switching valves, on/off valves, and pump systems which can be incorporated into the design of the implanted DDS of the current invention. For example, the connection means and flow controllers which serve to guide fluid from the reservoirs to one or more catheters can be embodied in a very thin silicon-based or elastomeric multilayered plate which is functionally connected to the reservoirs and one or more catheters. While the relatively small size of the microfabricated elastomeric valves and pumps can not provide the pressure, resistance, or responsiveness needed for a system which uses catheters to deliver drugs to sites distal to the pump, the microfabricated components can used in conjunction with the larger components of the implanted DDS to deliver precise amounts. In this manner a hybrid micro/macro network is utilized by the drug delivery system, where the microstructure feeds the larger components which are capable of dispensing the drugs more efficiently and at greater pressures.

[**0084**] The medical drug delivery system contains a method for delivering a drug bolus functions by having at least one active drug and a pusher substances, each of which are output from their respective reservoirs consecutively. For example, a given dose of drug is dispensed from a Res**114***a* into the catheter. This drug takes up $\frac{1}{8}^{th}$ of the entire catheter length. The Res**214***b* holds an inert solution, which may be a diluent, but which in this application serves as a pusher fluid which acts to push the drug from Res**114***a* down the remaining length of the catheter, so that it is delivered as a bolus of a certain strength to the target located at the distal end of the catheter. The amount of pusher fluid that is dispensed is sufficient to send the drug through the distal end of the catheter and is calculated based upon the length and radius of the catheter. Utilizing a neutral fluid buffer has several advantages. When a certain dose is required by the target, normally the drug which has been dispensed earlier must clear the entire length of the catheter. By using a buffer fluid and buffer mode, only the specific amount of drug that is required is delivered to the target. Further, the system may be made more efficient by operating the pumping means for the buffer reservoir in a reverse manner, after the drug is delivered, in order to draw the fluid back into the buffer reservoir in order to use as little of the buffer solution as possible. The dual catheter designs may assist this type of operation.

[**0085**] A DDS can be implemented in a microchip such as those being developed by Microchips Inc (see US pat application 2003/0105455 by Santini). Current microchips are designed as a series of reservoirs or "wells", each of which is reversibly "capped" with a reservoir cap which can oscillate from an "open" or "closed" state depending upon, for example, an electrical charge applied to the cap. In the next section, the term DDS can refer to the DDS **10**, some embodiments of which are shown in **FIGS. 1***a*-**1***c*. Alternatively, the DDS can take the form of a microchip, a drug eluting stent, a constant rate pump which may be active or passive, an osmotic pump, or may be any other generic type of DDS **6** which is configured to provide therapy to the fetus, as is shown in **FIG. 3**. The DDS, as described below may be realized in a distributed form, and may have some components located external to the pregnant female. The DDS **6**, represents drug delivery devices and systems for providing drug therapy, and can include the DDS **10**, specifically described herein.

[**0086**] Systems and Methods of Modulating the Fetal Environment

[**0087**] Some characteristics of the drug delivery operations will be similar across many of the different medical treatments. One general method of using the DDS described in the prior section, or other embodiment of a drug delivery device (e.g., a generic DDS such as a constant flow pump),

to treat a medical disorder includes the steps of: implanting one or more sensors in the body of an implantee; sensing data from one or more sensors to generate sensed data; processing the sensed data to produce processed data; and, evaluating this processed data, using an evaluation routine, which produces either a positive result, wherein drug delivery occurs, or a negative result, wherein drug delivery does not occur.

[0088] When drug delivery occurs, it can be accomplished according to a drug delivery protocol. The drug delivery protocol can determine the site, drug, volume, rate, concentration, and type of delivery method (e.g. continuous, bolus, etc). In multiple catheter embodiments, the drug delivery protocol can determine the particular catheter and the site of delivery from that catheter for at least one drug. Additionally, when several catheters are provided, the drug delivery protocol can indicate which of one or more of the catheters will dispense drugs and in what temporal order. When each of the catheters is capable of delivering more than one drug, the drug delivery protocol will also determine which drug should be sent out of each catheter. When electrical stimulation leads are also utilized by the DDS, these can stimulate electrically, according to an electrical stimulation protocol (which can also be stored in the database of the delivery system), to work in conjunction with the drug delivery to achieve a desired result.

[0089] The sensed data can be data sensed by sensors, for example, electrical (e.g., EEG/EKG/EMG), pressure, flow, optical, chemical, and biosensors. The sensors can be configured to obtain signals related to at least one patient. In some applications the patient may be either a mother (taking into account the effects that treatment of the mother has on the fetus) or fetus, or both the mother and the fetus may be treated. The processing, utilized to process the sensed data into processed data, can comprise signal analysis, for example, signal averaging, filtering, spectral analysis, wavelet analysis, pattern recognition, modeling and simulation, and may include statistical analysis. Alternatively, the processing may comprise operations as simple as making the sensed data available so that it may be stored as at least one value in a table of the database used by the software program which controls the drug delivery operations. The processed data can be submitted to an evaluation routine and evaluated in order to determine whether a positive or negative result has occurred. A positive result can occur if the evaluation protocol determines that some characteristic of the processed data meets (or fails to meet depending upon the comparison operation used by the evaluation routine) specified criteria. For example, the evaluation of processed data may indicate that the concentration of a metabolite, associated with increased chance of labor, has met criteria which concern a specific concentration level existing for a specified amount of time. The evaluation protocol can include comparing processed data to data stored in a population/normative values table RT**3** of the database of the DDS. Rather than using sensed data, the DDS can also deliver therapeutic substances strictly according to a predetermined regimen that may be aimed towards providing prophylactic or other therapeutic results.

[0090] The medical drug delivery systems and methods described herein can be used in many clinical applications. Several examples of applications relating to using this technology to assist in promoting healthy labor and development of the fetus will now be discussed. It is understood that these methods can be used with the DDS described in detail earlier, or can easily be used with other types of a drug delivery devices (e.g., generic implantable drug pumps such as the programmable or continuous drug pumps made by Medtronic, Minn., one of which is the SynchromedII), depending upon the treatment needs of the fetus. The systems and methods can be used prior to pregnancy, during pregnancy, or acutely during birth.

[0091] In one method, at least one sensor, such as a biosensor, is implanted into, or proximate to, a region such as the womb, the amniotic sac, the maternal side of the placenta, the fetal side of the placenta, in or near the arterial or venous passageways of the umbilical cord (or respective areas of the chorion plate), the placenta, or the uterus, and the drugs are delivered in response to evaluation of the sensed data that are sensed by these sensors. For example, if the umbilical venous blood supply is lacking in a specific nutrient, blood gas, or hormone, or if the supply is not flowing at a normal rate, then the DDS can dispense drug to compensate for this abnormality.

[0092] The DDS can provide therapeutic benefit by, for example, delivering drugs, neutralizing toxins (e.g., though filtering, chemical/molecular transformation of, or binding with, the toxin), removing harmful substances from the fetal environment through passive or active shunting, and performing other operations in response to sensed data, due to a delivery regimen, and/or in response to commands sent by an external patient programmer. More specifically, in addition to delivering fluids, the DDS can also remove fluids, or filter fluids transported to or from the fetus, for example, via the umbilical cord or amniotic fluid, and can also filter fluids in the body of the implantee. In one method, the DDS removes or alters fluids of the fetal environment which may be harmful to a developing fetus. For example, since the components of the amniotic fluid can affect the fetus (the fetus can swallow and urinate into this fluid), the DDS can pump or shunt amniotic fluid to a distal location ("shunt mode") and causing more amniotic fluid to be made, thereby diluting the concentration of the harmful substance if this enters the fluid at a rate less than the generation of new fluid. Alternatively, the DDS may filter a fluid, such as the amniotic fluid, before returning it to the same or similar location ("filter mode"), and thereby remove undesirable filtrate such as, for example, heavy metals which are thought to contribute to neurological disorders such as autism (e.g., Bernard, 2002). The term "filtered fluid" can refer to fluid which is physically filtered or can refer to the neutralization of a substance through chemical, electrical, or molecular alteration which functionally removes an unwanted characteristic of a substance, including dispensing a drug which competitively binds to the caustic substance. The DDS may also operate in a "push-sample" mode to send samples of the amniotic fluid to a distal site so that these samples can be analyzed by various laboratory procedures. The DDS can also use the push-sample technique to discard filtrate which it has stored temporarily ("purge mode") to a distal location in order to inhibit too much filtrate from building up in the DDS.

[0093] Removal or transformation (e.g., via competitive binding) of various substances in the fluids of the uterus, placenta, umbilical cord, and amniotic fluids can aid in treatment of various disorders. The DDS can assist in

removing/transforming carbon dioxide, bicarbonate, lactic acid, and hydrogen ions (or may dispense drugs which alter or chemically bind to these substances), and thereby assist in the protection against acidosis. This can be accomplished via electro-chemical or chemical changes produced within specialized structures, such as a filter. Alternatively, the DDS can deliver drugs which assist (modify), intrinsic biochemical operations or cellular activity which occur, for example, in the placenta in order to increase its transfer of certain substances. The DDS can deliver drugs which assist in the binding of oxygen to fetal hemoglobin, or can deliver drugs, such as 2,3-diphosphoglycerate (2,3-DPG), which change the affinity of the (adult) hemoglobin for oxygen, thereby increasing the transfer of oxygen across the placenta. When 2,3-DPG rises, in response to anemia or hypoxia, it binds to and stabilizes the deoxygenated form of hemoglobin, resulting in a shift of the oxygen dissociation curve to the right. Increasing 2,3-DPG on the maternal side of placenta and decreasing it in the fetal blood will lead to increased oxygenation. Using the DDS to deliver drugs which manipulate PH can also increase transfer/binding of gases within hemoglobin. Using the DDS to pump or re-route maternal blood traveling towards the placenta can also compensate for reduced placental perfusion and the consequent decrease in fetal arterial blood oxygen content due to low pO2 (hypoxemic hypoxia).

[0094] The DDS can function in several additional manners or modes which have not described previously. For example, a flow compensation mode refers to the DDS assisting in pumping fluids within existing structures and vessels, for example assisting in the transfer of naturally available fluids through an artery or vein, or pumping stored fluids through these structures. The DDS can use flow compensation to assist in treating abnormalities of feto-placental flow within the umbilical cord. Flow redirection refers to the DDS serving as artery or vein and redirecting fluids from one part of the implantee's body to a different part of the body to assist, for example, in correcting abnormal vascularization of a structure such as the placenta. The DDS can deliver fluids which assist the activity of biological structures such as the placenta in maternal-fetal transport of, for example, nutrients or oxygen or help in the physical or metabolic elimination of, for example, carbon dioxide or fetal metabolites.

[0095] The maternal-fetal circulation may be conceptualized as two fluid circuits that affect each other via the placenta. From a pharmacological (model) standpoint the anatomical structures and fluids of the mother are considered a maternal compartment, the anatomical structures and fluids of the fetus create the fetal compartment, and the anatomical structures and fluids in the placenta can be conceptualized as a placental compartment. Both the maternal and fetal sides of the placenta have afferent structures which carry fluids towards the placenta, and efferent structures which carry fluids away from the placenta.

[0096] The term "maternal afferent structure" refers to structures that move fluid towards the fetal side of the placenta and away from the mother such as the internal iliac arteries, utero-placental arteries and structures within the basal plate of the placenta

[0097] The term "maternal efferent structure" refers to structures that move fluid away from the the placenta and towards the mother, for example, the utero-placental veins.

[0098] The term "fetal afferent structure" refers to structures which move fluids from the fetus towards the maternal side of the placenta and, for example, the umbilical arteries and the placental villi which feed them.

[0099] The term "fetal efferent structure" refers to structures which move fluids to the fetus from the maternal side of the placenta are such structures as the umbilical vein, the areas of the chorion plate to which the vein attaches, and other structures.

[0100] The term "intra-uterine target" refers to any structure in the uterus. The term "uterine afferent" refers to any structure, including supporting vasculature which brings fluids to the uterus and its related structures. The term "uterine efferent" refers to any structure, including supporting vasculature which carries fluids from the uterus and its related structures.

[0101] The term "related characteristics and processes" refers to physical (e.g. flow rate), chemical (e.g., amount of a hormone), biochemical, molecular, metabolic, anatomical (e.g. structural, developmental), physiological (e.g., transfer of a substance across a membrane) or other characteristics or processes which are related to the input of, output from, or flow within a structure.

[0102] The DDS can deliver drugs based upon data sensed from sensors that can measure, for example, intrauterine pressure, intra-umbilical pressure or flow rate, fetal heart rate, and maternal factors such as the mother's heart rate, blood concentration of a substance such as C-reactive protein, or glucose level. The systems of drug delivery can use biosensors for sensing the composition of at least the amniotic fluid, umbilical vein, umbilical artery, maternal blood, or other sensors for sensing maternal EKG, fetal EKG, or fetal EEG. The sensors can sense blood gases such as oxygen, or PH, or sound (e.g. using a fluid-proof microphone). The sensors can incorporate or be in communication with microdialysis probes and analysis systems.

[0103] The sensors can sense a physical, chemical, biochemical, molecular, physiological or other change in at least one structure moving fluids towards or away from the fetus. Sensors can be located in any of the afferent or efferent structures and can sense the related characteristics and processes of these structures. Sensors can also be located in the placental compartment, maternal and fetal compartments, including in the amniotic fluid. Sensors can also be located within the mother and/or within the fetus. Drugs can be delivered to any of the afferent or efferent structures and can also be delivered to the maternal and fetal compartments, including into the amniotic fluid. Sensors can also be located in, and drugs can be delivered to, other intrauterine targets. The sites of drug delivery can be the same as or different than the locations of the sensors.

[0104] By comparing sensed data from afferent and efferent structures, either on the maternal side or on the fetal side, input/output indices can be generated. For example, ratio indices based upon sensed data from the utero-placental arteries and veins provide information about what is being transferred across the placenta, and indices based upon sensed data from the arterial and venous passageways of the umbilical cord provide information about what is being metabolized by the infant. Additionally, creating indices from data sensed from the maternal afferent structures and

the fetal efferent structures can provide measures of maternal-fetal transport. Further, indices can be created using sensed data from afferent and efferent structures on both the maternal and fetal sides of the placenta. Several examples, demonstrating the usefulness of some of these input/output indices, or other indices or ratio measures, will be discussed with respect to different medical disorders.

[0105] In one embodiment of the technology, a method of providing medical treatment to a fetus comprises delivering drug to a maternal afferent structure based upon sensed data sensed by at least one sensor located to sense at least one characteristic of fluid in at least one of the following locations: a maternal afferent structure, a maternal efferent structure, a fetal afferent structure, a fetal efferent structure, the amniotic sac, the placenta. The delivery of drugs used in treatment can, for example, produce a therapeutic effect by providing the fetus with a drug needed for the treatment of a medical disorder, but can also produce a therapeutic effect by causing a, physical, chemical, biochemical, molecular, physiological or other change in an afferent or efferent structure moving fluids towards or away from the fetus, as well as within the fluids themselves.

[0106] One embodiment is shown in **FIG. 3***a* where a drug pump **6** is shown implanted in a mother for drug delivery to the fetus. Although the potential structures from which data can be sensed include the structures of the maternal compartment **804** (including maternal afferent structures **812**, maternal efferent structures **808**), structures of the fetal compartment **832** (fetal afferent structures **824**, fetal efferent structures **820**) and structures in the placental compartment **816**, or in the fetus itself **828**, sensors **21***a* and **21***b* have been implanted to sense information from a maternal afferent structure and a fetal efferent structure, respectively. Data from the sensors **21***a* and **21***b* are sent back to the drug pump **6** via the data link **90** which is implanted in a catheter which delivers fluids related to therapy from the drug pump **6** to a delivery target located in a structure within the placental compartment **816**. One embodiment of a method of using a drug pump such as the DDS to treat a fetus is shown in **FIG. 3***b* and includes a series of steps which are repeated as therapy occurs. The step of sensing data **840** comprises sensing data from the sensor **21***a* in the maternal afferent structure **812** and from the sensor **21***b* in the fetal efferent structure **820**. The step of performing an evaluation routine to evaluate data **824**, which can include processing the sensed data using signal analysis to obtain processed data which is then evaluated to produce a positive result **858** or negative result **852**. In the case of a positive result **858**, drug delivery occurs and drug is delivered through the catheter to the placenta. When the drug pump **6** is the DDS, drug can be evaluated using evaluation routines **320***e* which compare the sensed data to normative data stored in the population/self normative values table Rt**3** of the database **322** delivered according to a drug delivery protocol which is based upon values contained in the delivery routines/protocols table Rt**4** of the database **322**.

[0107] The DDS contains algorithms and signal processing routines for automatically processing the sensed data into processed data. For example the fetal EKG, signal can be processed in order to obtain a meaningful measure such as inter-beat interval. Other characteristics of the fetal EKG can be the variability of the inter-beat-interval, or the classification of the fetal EKG signals into normal/abnormal beats using, for example, template matching algorithms. Measures such as rates of change may also be obtained, for example, which can be a useful measure when assessing whether contractions of the uterine muscles are occurring more rapidly within a given time interval. The signal processing of the sensed data used to obtain the processed data can include operations which enable transforming sensed data into meaningful units, and the creation of statistical summaries, ratios, classifications into abnormal/normal data, and for making computations upon characteristics such as rates of change, and for filtering, frequency analysis and other operations known to those skilled in the art of signal processing and statistics.

[0108] The sensed data and processed data can be evaluated, and based on this evaluation, at least one drug can be delivered to at least one site. Performing an evaluation of sensed/processed data may include comparing the values of the sensed/processed data to reference data which can be normative data such as a self norm from a previous time or set of times, or an age and sex appropriate population norm. The outcome can be a pass/fail result and can be determined by threshold criteria or statistical criteria and may be a score, such as a Z-score which indicates the statistical likelihood of abnormality. Performing an evaluation of sensed/processed data may also include using the values of the sensed/processed data from the umbilical vein and the values of the sensed data from the umbilical arteries to compute an input/output function (c.f., Osada et al, 2002) for at least one sensed substance and includes comparing this input/output function to normative data which may be a self norm from a previous time, or set of times, or an age/sex appropriate population norm, and the outcome is determined by threshold or statistical criteria. The evaluation of sensed data can result in the detection of a medical event, which is any pattern or characteristic of the sensed data which indicates that drug delivery should occur.

[0109] Depending upon the physiological, chemical, or other factor that is being measured, sensing of measures can range from thousands of times per second (e.g., measurement of EKG) to once a day or less. Comparisons of these measures with normal values can be based upon the measures themselves, or may be based upon transformations of these measures. For example, the absolute measures of arterial or venous flow can be evaluated, or these may first be normalized, for example, in relation to fetal abdominal or head circumference. Some measures can be evaluated with respect to (i.e., within the context of) other changes exhibited by the fetus (e.g., changes in the EKG can be evaluated with respect to measures of apnea, a pulsitility index, oxygen/NO/CO_2 levels), or in the fetal environment (e.g., during periods of quiescence or during uterine contractions). Measures may be z-transformed against reference values as has been described by the inventor previously (e.g., U.S. Pat. No. 6,463,328, incorporated by reference herein) and the results can be used to enable the drug delivery system to work in a closed loop capacity. Accordingly, the fluids can be dispensed until certain criteria are met (or only if certain criteria are met), or delivery may partially or fully be a functionin of user intervention. In this latter instance, the DDS can send information to the external patient controller so that an implantee or doctor can evaluate the sensed data and choose an appropriate intervention.

[0110] A database containing normative values which are related to the development of the fetus is useful. When the drug pump is the DDS **10**, the normative values can be contained in the population/self normative values table Rt**3** in the database **322** and can be normative data for any location in which the sensor can be placed and can contain normative data for the characteristics which may be sensed by the sensors. Additionally the population/self normative values table Rt**3** of the database **322** can contain statistical values for the normative data that are related to the sensed measures. Normative data can come from a healthy population, from a population which suffers from a similar disorder as the disorder for which treatment is being provided, or from the individual. The database should contain normative values that change with the age or development of the fetus. For example, Kwon et al (2003) have reported developmental changes in concentrations of amino acids in ovine maternal arterial plasma, fetal umbilical venous plasma, and fetal fluids. Three unique, major findings emerged from this study: 1) Ovine fetal:maternal plasma ratios for amino acids changed greatly during gestation, 2) the marked changes in concentrations of amino acids in ovine allantoic and amniotic fluids were associated with conceptus development (for example, concentrations of alanine, citrulline, and glutamine in allantoic fluid increased by 20, 34, and 18-fold, respectively, from day 30 to day 60 of gestation and were approximately 80, 30, and 60-fold, respectively, those in fetal plasma on day 60 of gestation), and 3) alanine, citrulline, and serine were unusually abundant in ovine allantoic fluid compared with any other biological fluid in animals suggesting important utilization of these amino acids by the fetus. Kwon et al also reported ovine fetal:maternal plasma ratios for amino acids throughout the entirety of gestation. Fetal:maternal plasma ratios for glutamate and serine were remarkably low and high, respectively, during late gestation. Since in vivo studies have demonstrated that little uterine uptake of glutamate occurs from maternal plasma, but that placental uptake of glutamate occurs in the ovine fetus, the authors conclude that extensive placental catabolism of glutamate and a high rate of fetal utilization of glutamate likely are the major factors responsible for its low concentrations in fetal plasma compared with maternal plasma. This study demonstrated that substances, such as amino acid levels, change over time in a manner related to fetal age and development. Additionally, the results suggest that a decrease in the allontoic:plasma concentration could be used as an index reflecting a disorder, for example, a problem with fetal absorption of an amino acid. Accordingly, the database can contain normative values for concentrations within a specific fetal structure such as the allontoic sac and can also contain indices (e.g. ratios) created using concentrations of substances from two or more areas or fluids (e.g. an allontoic fluid:fetal plasma ratio).

[0111] The database can contain normative values for levels of substances in the maternal compartments, the fetal compartments and can contain normative measures for ratio of levels of substances between these two compartments. Further the database can contain normative measures for structures within each of these two compartments such as afferent and efferent structures and their supporting vasculature. Normative values can be values from a population which may be matched for characteristics such as age, weight, volume, developmental period, metabolism, flow rates and volumes of maternal or fetal fluids, or for levels of substances which are detected by sensors which are related to the drugs being released. Normative values may also be self-norm values which are calculated based upon past values sensed for the fetus, the mother, or a combination or ratio of values for the fetus and the mother. The database can contain values which are derived from algorithms, equations, statistical measures and models which utilize the information stored in the database. For example, the database can contain a set of z-scores which can be computed from past sensed data and to which current sensed data can be compared. The data can be sensed data which is sensed by sensors of the DDS and can relate to presence, absence, or concentration of a substance, pressure, flow rate, fetal heart rate, or can be data obtained via external instrumentation operated by medical personnel or data obtained from analysis using laboratory techniques which have been sent to the database from an external patient controller. The database can be contained in the DDS or can be contained in an external patient controller or specialized computer which has communication means for communication with the implanted DDS.

[0112] The database can provide reference data values which are accurately related to the development of the fetus based upon single or multiple and direct indices or indirect indices. For example, fetal weight will increase similarly to allontoic fluid volume and amniotic fluid volumes. Accordingly, rather than measuring fetal weight, amniotic fluid volumes can be used to estimate the development or age of a fetus. The developmental stage or gestational age of the fetus can also be estimated using biochemical measures which can be absolute levels of a substance (e.g., absolute levels of glutamine) or ratio measures (e.g., glutamine-to-glycine ratio). Further, ratio's of substances which are sensed at two or more different structures can be used, such as the ratio of the concentration of a substance in the amniotic fluid compared to its concentration in the allontoic fluid.

[0113] Drug delivery can entail the delivery of therapeutic fluids such as vitamins, medications, growth factors, antioxidants, nutrients, amino acids, proteins, peptides, hormones, steroid products, and drugs which modulate the availability or metabolism of these substances. Amino acids serve as essential precursors for the synthesis of proteins, peptides, neurotransmitters, aminosugars, purine and pyrimidine nucleotides, creatine, carnitine, porphyrins, melatonin, melanin, sphingolipids, polyamines, and nitric oxide. Amino acids also function as antioxidants, regulators of hormone secretion, major fuels for fetal growth, and signaling molecules. In particular, glutamine plays an important role in fetal nitrogen and carbon metabolism. Polyamines, synthesized from ornithine are essential to placental development and mammalian embryogenesis. Nitric oxide, synthesized from L-arginine, has enormous metabolic versatility and physiological importance, including potential roles in regulating placental angiogenesis and uterine blood flow during gestation. Additionally, serine and glycine are a main source of one-carbon units for cellular metabolism, including DNA synthesis and methylation. Since amino acids play a vital role in the growth, development, metabolism, and immune response of the conceptus, and in processes related to the maintenance of pregnancy, the DDS can modulate this by dispensing amino acids or substances that affect their metabolism.

[0114] There is ample evidence that an adverse intrauterine environment has harmful consequences for health in later life. Medical conditions such as metabolic disorders of the mother are one source that can contribute to a less than optimal environment. Further treatment of maternal disorders can also introduce substances and their metabolites which enter into the fetal environment. In disorders of maternal deficiency (e.g., nutritional deficiency such as iodine, iron, and other vitamins and minerals) or maternal metabolic disorders (e.g., thyroid disorders, diabetes, lupus) the DDS can provide direct or local delivery of therapeutic substances to aid in supplementation, compensation, or normalization of maternal-fetal fluids and the fetal environment and in the treatment of the fetus with respect to these abnormalities.

[0115] The DDS can assist in pregnancy where the mother suffers from a medical disorder such as diabetes, gestational diabetes, or other condition which results in insulin dysregulation, hyperglycaemia, or hypoglycaemia. As reviewed by Holemans et al 2003, both maternal diabetes and experimentally induced hyperglycaemia result in asymmetric overgrowth, due to an increased supply of glucose and other nutrients (Freinkel, 1980), which is associated with increased insulin secretion and hyperplasia of the insulin-producing B-cells in the fetus. As a result, in adult life, a reduced insulin secretion may occur. In contrast, intrauterine growth restriction is associated with low insulin secretion and a delayed development of the insulin-producing B-cells. These abnormalities in the fetal environment may induce a deficient adaptation of the endocrine pancreas and insulin resistance in later life. While intrauterine growth restriction in human pregnancy is mainly due to a reduced uteroplacental blood flow or to maternal undernutrition it can also be due to severe diabetes complicated by vasculopathy and nephropathy. Additionally, moderate or sever diabetes can interact with other factors in the fetal environment to produce hyperinsulinaemia or hypoinsulinaemia. Animal models have verified that intrauterine growth retardation can be obtained through pharmacological, dietary, or surgical treatment of the mother (arterial ligation). The endocrine pancreas and insulin-producing B-cells assist in the fetus' adaptation to an adverse intrauterine environment and this adaptation seems to have consequences after birth. Accordingly, the DDS of the current invention can be used to regulate levels of such substances as blood glucose by dispensing hyperglycemic and hypoglycemic hormones (e.g. insulin), or substances which will aid in the proper fetal metabolism of glucose, or substances which will affect the transfer (e.g., substances which will competitively bind to glucose transporters) of glucose across the placenta in the maternal-fetal or fetal-maternal direction, or enzymes involved in glucose metabolism, or genes or drugs which influence insulin secretion, absorption, binding, or metabolism in the maternal or fetal blood. The DDS can rely on sensors which sense the maternal blood either near the placenta, systemic levels (i.e., a glucose sensor in the arm of the mother) or both, and can dispense medication either next to or within the placenta or fetal compartment.

[0116] The DDS can assist in pregnancy where the mother suffers from a medical disorder such as hypothyroidism. For example, the DDS can sense local concentration of thyroid hormone near the fetal-placental unit (FPU) and dispense this hormone to keep levels within normal limits. Studies (e.g., Haddow, et al, 1999) have described mental defects occurring in children born to mothers with untreated hypothyroidism. Hypothyroidism is relatively common, occurring in about 1 in 100 women during the child-bearing years. It becomes more common with age, a feature which is relevant since women are increasingly deferring pregnancy. Since the developing fetus is unable to make its own thyroid hormone during the early stages of pregnancy the thyroid hormone must be transferred from mother to fetus across the placenta until the fetus' own thyroid gland starts to function during the second trimester. Even then, it is important that thyroid hormone levels made available to the fetus is well regulated. Accordingly, the DDS can assist in sensing hormone levels and modulating these by dispensing drugs to keep these levels within a desired range.

[0117] The DDS can assist in pregnancy where there is a hypoxic disorder whereby the fetus does not obtain normal levels of oxygen due to, for example, flow disorders where the flow in the umbilical cord is decreased compared to normal levels. Biological disorders which affect the availability of oxygen to reach the fetus are similar to internal hypoxic events which occur in individuals after birth. These events can affect the developing brain in a manner similar to a stroke and can affect other organs, such as the heart, similar to ischemic factors such as buildup of plaque in the supporting vasculature. Stroke is a loss of brain function resulting from interference with the blood supply to the central nervous system (CNS). CNS damage occurs in stroke as a result of hypoxia and decreased glucose availability. In the case of a transient ischemic event where oxygen supply is only briefly interrupted, the DDS can assist in lessening the effects of this event by responsively dispensing medication. For example, the effects of increased amounts of free radicals are lessened by dispensing neuroprotectants such as antioxidants. Antioxidants are natural or synthetic compounds which produce therapeutic effects in several ways including the removal of O_2, scavenging reactive oxygen species or their precursors, inhibiting reactive oxygen species (ROS) formation and binding metal ions needed for catalysis of ROS generation. In more chronic hypoxic conditions, the DDS can provide prophylactic treatment whereby the detrimental effects of a continuous deficiency are decreased. The effects of hypoxia on the CNS are very complex and involve mechanisms which can be compensated for by delivery of drugs, such as energy failure, loss of cell ion homeostasis, acidosis, increased intracellular calcium, excitotoxicity, and free radical-mediated toxicity, all of which contribute to ischemic necrosis and apoptosis, which are associated with factors such as loss of calcium and glutamate homeostasis (Gilgun-Sherki et al. 2002). One main objective of dispensing drugs to the fetus in response to a hypoxic condition is to decrease the effects of free radicals and harmful second messenger cascades. Free radicals (oxidizing agents) are highly reactive molecules generated predominantly during cellular respiration and normal metabolism. When the fetal environment supplies less oxygen than is needed, an imbalance between cellular production of free radicals and the ability of cells to defend against them (by antioxidant protective systems which create and upregulate the substances) may occur and is referred to as oxidative stress (OS) which is implicated in the pathogenesis of acute central nervous system (CNS) injury. The hypoxic event may increase the production of reactive oxygen species (ROS), sometimes drastically, leading to tissue damage via several different cellular molecular pathways. Accord-

ingly, treatment with antioxidants will prevent propagation of tissue damage and improve both the survival and neurological outcome. Since the effects of the free radicals are related to the hypoxic event, it is important in the case of transient hypoxic events that the DDS supply the antioxidant drugs temporally close to the time of the hypoxic event and within the "neuroprotective window". Novel combinations of drugs providing protection against various types of injuries should exploit the potential synergistic effects of antioxidants and receptor modulators in stroke (e.g, US 20020123510).

[0118] By sensing or otherwise determining the oxygen levels which are available in the fluids supplying the fetus (e.g., via sensing umbilical flow rates or changes in metabolites in fluids leaving the fetus) and dispensing drugs which minimize the effects of free radicals, the DDS can greatly attenuate the risks associated with hypoxic conditions. Further, by sensing "specific markers of cerebral injury" such as proteins or polypeptides that are associated with brain tissue and neural cells, and which can be correlated with a cerebral injury, the DDS can monitor if the dispensed drugs are adequate and adjust the delivery regimen accordingly. For example, the drugs should be appropriate to the precise OS physiology (e.g., the type of ROS involved, the place of generation, and the severity of the damage) and the fluids of the fetal compartment may contain metabolites which indicate a specific type of OS has occurred. It is obvious that similar to the brain, other organs, such as the fetal myocardium, can also be protected from hypoxia or other conditions which lead to increases in free radicals, using antioxidants and calcium antagonists such as Anipamil. Drugs which can be delivered by the DDS to protect against damage due to free radicals can include drugs which promote the transcriptional up-regulation antioxidant substances in fetal cells, decrease the production of extracellular glutamate (e.g, by blocking the presynaptic release of glutamate and/or by blocking the excitation of postsynaptic neurons), ROS scavengers, calcium channel antagonists, cytokines, vitamins C and E or analogs (OPC-14117, MDL 74,722), melatonin, ascorbic and lipoic acids, polyphenols, and carotenoids, superoxide dismutase (SOD) and catalase (CAT), metal ion chelators, Glutathione, YM737, Creatine, spin-trap scavenging agents, etc.

[0119] The DDS can also assist in pregnancy where the mother is exposed to drugs, which are noxious to the infant, either through drug abuse or due to treatment of a medical condition. For example, delivered substances could counter the effects that maternal drug abuse treatment may have on the fetus. Naltrexone is a narcotic antagonist that blocks the opioid receptors in the brain. Naltrexone also blocks the reception of the opioid hormones that our brain and adrenal glands produce: beta-endorphin and metenkephalin. Many body tissues have receptors for these endorphins and enkephalins, including virtually every cell of the body's immune system. Opiod peptides serve as a negative regulator of growth, cell migration, differentiation, and survival. Blockade of opioids by opioid antagonists such as Naltrexone (NTX), results in a stimulatory response. NTX is able to cross the placenta and can be identified in fetal tissue. This can lead to increased organ weight and development in infants. Accordingly, the repercussions of using NTX in the treatment of alcoholism and drug abuse in pregnant mothers may be long-lasting and significant for the offspring. The implications are twofold. Firstly, in the case where a mother is undergoing treatment with NTX during pregnancy, the DDS could compensate for exposure to NTX through supplementation of opioid compounds. Additionally, since NTX can cause an increase in heart cells and the size of the heart (McLaughlin, 2002), NTX can be delivered by the DDS to augment growth in a fetus with congenital heart disease. By sensing the amounts of opioids or opioid antagonists in the fetal blood, and comparing these values to normative data, compensatory drug delivery may occur to lead to improved development of the fetus.

[0120] The DDS can be used to combat the effects of different drug treatments that a pregnant implantee may undergo such as treatment of metabolic disorders or psychiatric disorders such as depression. In one embodiment, the DDS uses a method of delivering one or more drugs to a mother which comprises limiting the total amount of drug delivered with respect to a specified amount of time, said limit being based upon data relating to the infant, or to both the mother and infant. This method is different than that of the prior art which delivers drug therapy based upon measures of only one patient (or implantee), rather than based upon measures derived from a second patient, or both the first and second patient.

[0121] The measures which can be sensed in order to modify drug treatment of the mother or compensate for this treatment by dispensing drug to the fetus create the sensed data. This sensed data is evaluated using information in a database **322** to determine if the data indicates that the drug related changes or the amount of drug to be dispensed are within acceptable limits. These limits can be based upon an equation or model whose variables include a history of past drug delivery and include characteristics of the fetus such as at least one of the following, absolute or relative levels of current or past sensed data, or changes in the levels of sensed data, or a combination of the two, said sensed data relating to measures of metabolic rate, metabolites, chemical or biochemical substances, or physiological events, or predicted gestational age, head volume, body volume.

[0122] The DDS can deliver therapy to treat fetal cardiac insufficiency due to persistent tachyarrhythmias. The DDS treatment can use medications which are currently given to the mother and therefore made available on a systemic level (e.g., with either digoxin alone or combined with other drugs) but can deliver these directly into the fetal compartment. Accordingly, the DDS can enable pregnancy to continue in preterm patients with risk of fetal cardiac failure and decreases mortality and morbidity.

[0123] Uteroplacental insufficiency is a major cause of perinatal mortality and complication in growth restricted fetuses (Di Naro, et. al. 2002). One major source of insufficiency is severely impaired feto-placental flow especially with respects to reversed blood flow in the diastolic component of the umbilical artery. Decreases in blood flow (and blood flow velocity) can be caused by decreases in the volume of the umbilical vessels or by increased viscosity of the material transported within these vessels (Jouppila et al, 1986; Drew et al, 1991) and leads to fetal compromise and complications. Raio et al (2003) found that all umbilical cord components (umbilical cord cross-sectional area, vein area, artery area, and Wharton jelly area) were smaller in intrauterine growth-restricted fetuses. The prevalence of lean umbilical cords (cross-sectional area <10th percentile

for gestational age) was significantly higher in intrauterine growth-restricted fetuses compared with appropriate-for-gestational-age fetuses.

[0124] By sensing blood flow in the umbilical artery or vein, one can detect abnormal flow, as compared to the expected flow for age matched normative data. Although monitoring of umbilical venous flow has been shown to have better diagnostic accuracy than umbilical artery flow, either measure, or an index based upon a combination of these measures, can be used to monitor flow and for comparison to normative values. In addition to an implanted sensor which senses flow, flow can be based upon Doppler waveform analysis (e.g., color Doppler velocity integration or velocimetry). The DDS can act to modify, supplement or normalize this flow and thereby compensate for insufficiency. For example, the DDS can act as a pump which assists in moving fluid towards or away from the fetus which exists either within or external to the umbilical cord. Additionally the DDS can deliver blood thinning drugs to increase umbilical flow or can deliver oxygenated fluid or nutrients to compensate for abnormal flow. Since absolute blood flow increases as a function of gestational age (Lees et al, 1999), the normative values can be based upon factors such as estimated gestational age, head volume, body volume (or weight) and other measures well known to those skilled in the art. The "normal" flow values may also be based upon the cross-sectional area of the cord or one of its lumen (Di Naro et al., 2002).

[0125] The DDS can assist in compensating for abnormal blood flow to the uterus, placenta, or through the umbilical cord. The DDS can assist and compensate for problems in maternal-fetal transfer and transport which can be due to many sources including morphologic abnormalities which may deteriorate placental oxygen and other nutritional transport. The measures which are used to sense abnormal function will vary depending upon the structures being evaluated, for example, abnormal uterine artery blood flow can be indicated by abnormal velocity waveforms which may be identified by a persistent abnormal index, a persistent diastolic notch or an abnormal difference between the indices in the left and right uterine arteries (Thaler et al. 1992).

[0126] The prevention of fetal hypoxic injury and acidemia is another goal of modern obstetric practice (Luttkus et al, 2002). In addition to monitoring of the fetal EKG, heart rate monitoring is possible using reflected red and infrared light which can be converted into saturation values. Variable fetal heart rate decelerations may indicate a problem such as hypoxia. Fetal blood oxygen saturation can be estimated from pulse oximetry carried out by placing sensors on the fetus, such as on the fetuses' cheek or forehead, or other appropriate area. Umbilical artery decreased pH (or increased base deficit, altered lactate concentration) indicates acidemia or other abnormality associated with oxygen transport imbalance and impaired systemic oxygen utilization. Samples of fetal blood, obtained from umbilical vein or artery, can be output with the sample-push mode so that blood can be examined in the laboratory using blood gas analysis techniques such as hemoximetry. Umbilical blood pH should also be monitored because acidosis can be caused of a number of important conditions, aside from hypoxia, such as sepsis. Umbilical cord pH and base excess are related to subsequent adverse outcome for both umbilical artery and vein (Victory et al, 2003).

[0127] Accordingly, in order to treat hypoxia or other uteroplacental insufficiency related to impaired feto-placental flow, the DDS can deliver medicants to the placenta or into the umbilical cord, such as substances to decrease viscosity of blood (e.g., EPA ethyl ester, PP-188 or "purified poloxamer 188", lipid-lowering drugs, and angiotensin converting enzyme) or anti-coagulants (e.g., Warfarin), and can deliver fluids such as oxygenated fluids, both toward or away from the fetus. The DDS can complement umbilical function by bypassing sections of the umbilical cord, or can replace umbilical cord function by transmitting fluids between the placenta and the fetus, or can assist in umbilical flow by pumping fluids within the umbilical vessels or can deliver or remove fluids to/from distal targets/sources.

[0128] The drug delivery methods and systems can be used to deliver appropriate gene therapy, provide nutrients to the fetus, and can be programmed to provide different drugs at specific concentrations and based upon different times during the pregnancy period and at different times in the prenatal period just prior to birth. The DDS can also be used for the promotion of fetal health by introducing vitamins and other types of dietary supplementation. The promotion of fetal health and the augmentation of the immune system of the fetus can be accomplished via administration of substances from the DDS, for example, antioxidants to counter the effects of free radicals, nutrients, vitamins to ensure proper growth, metabolism and immune system development, and antibiotics to deter fetal infection. The immune system of the fetus is modulated by the nutritional composition of the umbilical blood and thereby influences the ability of the fetus to respond to infections. Selenium depletion, which mediates immune response, in part, through glutathione peroxidases and thioredoxin reductase, has been shown to decrease T cell and panB cell proliferation, antibody titers, and natural killer cell activity (Dylewski et al, 2002). When selenium transfer, via the placenta or mammary glands is decreased, then selenium supplementation would act to increase the immune response of the fetus and neonate.

[0129] The DDS can also be used for the promotion of fetal health by aiding in gene therapy provided directly to the fetus, for example, via the umbilical cord. Gene therapy can be used in the case where the DNA of the fetus or parents indicates a predisposition for a genetic disorder. When metabolic screening and evaluation indicates gene therapy is warranted the DDS can greatly assist in the normal development of the fetus. Gene therapy can be accomplished by infusing the therapeutic substance into the umbilical vein either continuously, periodically, according to a treatment regimen, medical model, or in response to sensed data, and monitoring the effect through chemical sensors or by sending samples of the umbilical blood out using the sample-push mode. Some gene therapy will use several types of therapies in a sequential manner, for example, the therapy may change with fetal developmental, or, alternatively, the therapy may require the same therapy to be repeatedly administered over many months.

[0130] In one method of treating a fetus for a medical or genetic disorder, which is a simple embodiment of the invention, the DDS merely comprises an osmotic pump with

a catheter containing a tip that is appropriately configured to enable drugs to be delivered within a uterine structure such as the umbilical cord. For example, the DDS contains an attachment means to secure the DDS near the cord, and to secure the catheter within the cord. Alternatively, the DDS may be comprised of more sophisticated components such as an inlet catheter which can transmit fluid from the umbilical cord into the DDS which can be filtered before redeploying the fluid into the cord, for example, sending the filtered fluid back into the umbilical vein from which it was drawn. In order to avoid build up of the unwanted filtrate, the drug delivery system can periodically operate in a "purging mode" which acts to send said unwanted substance through a waste disposal means, such as a catheter that terminates far from where the filtered fluid was obtained, so that said noxious filtrate does not re-enter an area where it can affect the fetus. Fluids from within the womb may act as diluents or buffer fluids for the DDS, for example, when it operates in a recirculation/replenishment mode or in purging mode.

[0131] In one embodiment, a method of using the implantable DDS for treating disorders of a fetus includes: implanting a drug delivery system into a pregnant female; functionally connecting a drug delivery means, such as a catheter, into an umbilical vein of the umbilical cord; and using an attachment means to reversibly secure a portion of the drug delivery means within the cord.

[0132] The medical drug delivery device of the current invention can be used in other obstetric applications, for example, in order to prevent or discourage miscarriage and preterm labor, thereby extending the term of pregnancy. Currently, 6-10% of all newborns in the industrialized world are born preterm and so such an application is medically important. In order for the extension of pregnancy to be helpful, it does not require that an infant is carried to full term. Of babies born at 24 weeks gestation, only 20% survive, but by 30 weeks gestation survival increases to 90%, with survival increasing roughly linearly over that period (Ingemarsson and Lamont, 2003). At more than 10,000 per infant, neonatal intensive care annually costs about $5 billion in the United States. Accordingly, increasing the term of pregnancy by a couple of weeks may greatly improve the survival of the neonate and decrease a significant national medical cost.

[0133] In one embodiment of the system and method, if the DDS senses the onset of contractions or chemical change which may lead to contractions, miscarriage or preterm labor, a drug is released to attenuate or halt this process. The DDS can also achieve this goal by providing therapeutic agents to prevent or treat infections such as intrauterine or genital tract infection. A strong association between upper genital tract infections and preterm delivery (before 30 gestational weeks) has been shown (Andrews et al, 1995). Estimates are that 20-40% of preterm deliveries may be caused by infection (Gibbs et al., 1992) and bacterial sources (e.g., subclinical chorioamnionitis or bacterial vaginosis). Inhibition of such factors through localized treatment, in addition to or instead of systemic treatment which are currently implemented, will aid in inhibiting preterm delivery and other complications associated with pregnancy. DDS treatment may be initiated when intervention is indicated by various markers and diagnostic tests, or DDS treatment may be utilized prophylactically when a predisposition is known due to a patient's history (e.g., prior preterm deliveries).

[0134] The prevention or delaying pre-term labor can occur via delivery of such drugs as tocolytics which act to counter contractions and antibiotics which prevent infection. The incidence of pre-term labor can also be decreased by assisting and promoting good fetal health, which is a general goal of using the DDS in obstetric intervention. For example, the DDS can be used to decrease the effects of hypoxia and uteroplacental insufficiency as has been discussed. Further, the DDS can be used to decrease effects of oxidants created in response to fetal insult, can improve or maintain fetal health by vitamin and nutrient supplementation, can attenuate or combat the effects of toxins that may be present in the maternal blood, and can assist in gene therapy to correct or compensate for genetic factors that can lead to pre-term labor.

[0135] The DDS can inhibit labor by delivering therapeutic substances according to a predetermined regimen, or continuously, or in response to sensed data such as an increased EMG signal, pressure signal, or biochemical concentration, sensed by at least one biosensor, which indicates either an increase in contractions or in a biological process that will lead to contractions. For example, the DDS can perform signal analysis to determine if labor is being initiated by analyzing sensed data from EMG or pressure sensors using spectral analysis and pattern matching and comparing the results of these operations to a threshold, past data sensed by the DDS, or normative data, to determine if a positive or negative result has occurred. When several catheters are provided, evaluation of the sensed data can indicate which of one or more of the catheters will dispense drugs and in what temporal order. When each of the catheters is capable of delivering more than one drug the DDS will also determine which drug should be sent out of each catheter. When electrical stimulation leads are also utilized by the DDS, these can stimulate electrically to work in conjunction with the drug delivery. Prior art (e.g., US2002/0010494 "Uterus muscle controller" and US2003/0055467 "Smooth muscle controller)) has described using electrical stimulation to provide closed-loop control of uterine muscles for the inhibition of labor, but this prior art does not discuss using drug delivery, either alone or in conjunction with electrical stimulation in order to inhibit labor. While labor may be inhibited, this prior art does not address treating the causes behind the premature labor. Additionally, when drugs rather than electrical stimulation are used to inhibit labor the drug delivery protocol should be tailored to optimize drug delivery and this requires sending different drugs to different locations, or only out of a specific catheter that is proximal to the sensor which surpasses a specified criteria by the largest amount.

[0136] The DDS can assist in delaying labor and extending the pregnancy period by delivering drugs locally to specific targets, thereby decreasing the amount of drug needed to achieve effects. Tocolytics, which include oxytocin antagonists, cyclo-oxygenase inhibitors, calcium channel blockers, beta2 agonists, currently work well at inhibiting labor, but carry a large range of unwanted and serious side-effects. The DDS may be able to produce increased therapeutic benefit by locally (or in conjunction with maternal systemic delivery) delivering relatively low levels of

these myometrial relaxants when sensors indicate a need. For example, the DDS catheters can be surgically implanted to administer tocolytics to the blood supply of the myometrium or other structure of the uterus, for example, via the radial uterine arteries in order to inhibit uterine contractibility. In one method of the present invention, fluids such as competitive antagonists or substances which bind to unused tocolytics drug may be delivered subsequent to the delivery of tocolytics, or in other areas that are relatively separate from the uterine muscles, in order to functionally neutralize, counter or at least diminish the unwanted side-effects of, the tocolytics after they have produced their desired effect.

[0137] There are many markers that are associated with increased risk of pre-term labor and may serve to indicate candidates for DDS therapy. For example, elevated C-reactive protein (CRP) levels as measured in the maternal blood taken at the beginning of a pregnancy are associated with roughly a twofold increase in the risk of preterm delivery (Hvilsom et al., 2002). Additionally, increased vaginal fluid CRP concentration has been associated with intra-amniotic infection and funisitis (Di Naro et al, 2003). High ferritin and IL-6 levels in the amniotic fluid may server as markers of inflammation in asymptomatic women destined to have an early pregnancy loss (Ramsey et al, 2002). Further, elevated levels of interleukin-6 in cervical secretions and in amniotic fluid, ostensibly present in response to infection, has been shown to be correlated with preterm delivery and can be detected with a strip test (Lange et al, 2003). Hvilsom et al (2002) have shown that a high C-reactive protein level, as indicated by a serological test of the maternal venous blood at the beginning of a pregnancy was indicative of a nearly twofold increase in risk of preterm delivery. Prostaglandins, which can become elevated in response to infection, serve as a trigger for the initiation of labor. While the role of prostaglandins is clearer for labor than for preterm labor (Guinn et al, 1995), agents that serve as antagonists of prostaglandin production, or which bind to or modify prostaglandins so that they fail to signal appropriately should assist in the inhibition of preterm labor. Andrews et al (2003) showed that fetal fibronectin in cervical/vaginal secretions is correlated with silent upper genital tract microbial infection, and may serve for a predictive marker of disposition for spontaneous preterm delivery. Although a series of studies have shown that antibiotic treatments have not been successful in preventing females, identified by fibronectin or other tests tests, from avoiding preterm labor and other complications, this type of intervention using an implanted DDS used in conjunction with other localized therapy may be more effective. Elevated C-reactive protein (CRP) levels as measured in the maternal blood taken at the beginning of a pregnancy are associated with roughly a twofold increase in the risk of preterm delivery (Hvilsom et al., 2002). Additionally, increased vaginal fluid CRP concentration has been associated with intra-amniotic infection and funisitis (Di Naro et al, 2003). High ferritin and IL-6 levels in the amniotic fluid may server as markers of inflammation in asymptomatic women destined to have an early pregnancy loss (Ramsey et al, 2002). Hvilsom et al (2002) propose that self norm of C-Reactive Protein from early in pregnancy period could be more sensitive indicator of increased risk of preterm labor than absolute cutoff based upon population norms. Accordingly, past values of sensed data, contained as self-norm values in the database of the DDS, can assist in prevention of pre-term labor. Accordingly, in one method of the current invention the DDS is implanted when biological markers indicate a biological abnormality which leads to an increased risk of preterm labor. These markers are used to provide the DDS with appropriate drugs, to guide catheter implantation to provide delivery of drugs to appropriate sites, to guide sensor implantation to provide sensing of data relevant to the disorder indicated by the marker, to program the DDS with drug delivery protocols appropriate for the disorder, and to guide treatment.

[0138] Using the DDS to improve and assist pregnancy and the antenatal environment may offer considerable advantages for a host of current medical problems. By implanting a DDS which utilizes sensors, normative data (either population or self-norm values), simple modeling, and either open or fully-/partially-closed-loop control, appropriate substances can be locally dispensed. Through appropriate catheter placement drugs can be delivered directly into the umbilical cord, amniotic fluid, the components of the uterus and placenta, and the supporting vasculature or even directly into the organs of the fetus. Insufficient or excessive amounts of an environmental factor (e.g., blood pH, oxygen, nutrients) can be supplemented or compensated for in order to provide improved antenatal development. The provision of bolus delivery in response to an acute event, or low level continuous delivery which is relatively independent of maternal factors of metabolism, can be assisted by sensors which measure substances traveling both towards and away from the fetus or supporting anatomical structures in order to measure the effects of drug delivery and construct input/output functions for the modulated target system or organ. In time, surgical techniques will likely allow DDS delivery to bypass the umbilical cord, or other structures involved in carrying fluids to and away from the fetus, and deliver fluids directly into the developing fetus. However, even if fluids are delivered directly to the fetus, the substances moving through the umbilical cord should still be monitored in order to determine the metabolites that are being delivered and removed from the fetus by the natural mechanisms.

[0139] The DDS can be used after birth occurs to continue to assist in promoting the health of the newborn infant by modifying the mother's breast milk. The DDS system and methods of the current invention can be implanted so that the catheter tip is inserted into the mammary glands, and can function to add nutrients, enzymes, vitamins, and other substances to breastmilk. In one embodiment, a flow meter or other means can ensure that a specified amount of drug is provided throughout the day, which may be independent from, correlated with, or dependent upon the amount of breastmilk imbibed by the baby. According to an alternative method the breastmilk is measured, either by the DDS or by, for example, laboratory tests in order to determine its composition. The drugs delivery regimen is then adjusted according to the composition of the breastmilk, age of the infant, the nutritional/metabolic needs of the infant, medical tests performed on the infant or a combination of more than one of these factors. While prior art has described medical mixtures which can be given to the infant to improve its health, immune system, and antioxidant status, and which may be mixed with breast milk (e.g., US2003/0104078), the prior art does not describe using these mixtures in an implantable DDS, changing the mixture based upon the

needs or age of the infant, or changing the mixture based upon, or to compensate for, specific deficiencies in the mother's breast milk.

[0140] The DDS allows for continuous delivery of a variable concentration of drug, for Sequential Bolus dosing, for fluids to be pumped into the DDS where they can be filtered or modified, for multiple drugs to be accurately dispensed through a single catheter or multiple catheters, and for functioning according to the methods described herein to achieve advantages of drug delivery and treatment.

[0141] Implanted drug delivery systems have not been previously described which act to mechanically, chemically, or electrically or electrochemically filter (or modify or neutralize) fluids of the implantee in order to remove unwanted filtrate or decrease the harmfulness of the fluids components for the fetus. Further, the DDS describes removal of the filtrate using a purging mode so that a large abundance of filtrate does not inhibit the function of the device.

[0142] In one method of modulating the fetal environment for the treatment or prevention of fetal disorders, the disorders may include uteroplacental insufficiency, fetal hypoxic injury, academia, intra-uterine infection, and the intervention may be carried out using a programmable drug delivery system which senses data from at least one sensor configured to sense data from a pregnant female and/or a fetus. The sensors may sense data, for example, from a vessel of the umbilical cord, the placenta, or the maternal blood. In order to obtain different types of information which are relevant to drug delivery, the sensed data may be obtained from such sensors as a biosensor, a chemical sensor, an optical sensor, an electrode for sensing ECG and EEG signals, a PH sensor, a gas sensor, a flow sensor, and a pressure sensor. Further, sensed data may be obtained from external instrumentation that monitors either the mother or the fetus, or can be derived from laboratory techniques such as assays, or other techniques commonly used in medical/genetic laboratories The data is then evaluated to obtain a positive or negative result, and in the case of a positive result, the drug delivery device is then operated to cause either delivery of a medication, pumping (e.g., modulation of the fluids flowing to or from the fetus), or removal fluids through active or passive shunting. A positive result may occur if sensed data is evaluated to be above a given threshold value, or does not meet some other specified criterion which indicates that treatment (e.g., modulation of the fetal environment) is necessary. A positive result may occur, for example, if the sensed data is evaluated using signal analysis techniques and specialized algorithms, such as template matching, and the evaluated data indicates that a particular unwanted medical event, for example, pre-mature labor contractions, has occurred or is occurring. Other algorithms that may be used in the evaluation of the sensed data may include comparing sensed data to comparison measures such as a self norm (e.g., at least one value sensed previously from a sensor), a population norm (e.g., an appropriate reference value derived from a normative population), an absolute value, percentage value, or may be a comparison measure based upon a value calculated from several sensors or data sensed at several times, and may be evaluated by means of a ratio, multivariate equation, or model, such as an input/output function. Of course, the comparison measures must be appropriate for the developmental stage of a fetus, and accordingly these may be derived in relation to at least one of the following: age, gestational age, physical characteristics including fetal head or abdominal circumference, or body volume, maternal or fetal weight, and predicted age. The drug delivery treatment may be prophylactic, and may, for example, modulate (e.g., strengthen or assist) the immune system of the fetus, or inhibit of pre-term labor.

[0143] The drug delivery may consist of delivering many different agents to different targets. For example, tocolytics, oxytocin antagonists, cyclo-oxygenase inhibitors, calcium channel blockers, and beta2 agonists may be used to decrease the risk of pre-term labor. Additionally, antibiotics may be used to decrease incidence of intrauterine infection and abnormal bacterial levels, in response to sensed data, which monitors, for example, interleukin-6 or fibronectin in cervical secretions and in amniotic fluid, or C-reactive protein level of the maternal venous blood. As noted, selenium may be delivered to increase the immune system of the fetus, in addition to other therapy. In order to guide therapy more accurately, the drug delivery system may periodically operate in a sample-push mode in order to provide samples to medical personal which may be examined using laboratory techniques.

[0144] In the most simple form, the modification of fluid flow, which constitutes a method of treatment, can be achieved using a stent, a medicated stent, or a shunt. The shunt may either be passive or may contain a programmable valve. In alternative embodiments the drug delivery system may be fully implantable, partially implantable, and may rely upon external instrumentation for its sensing or dispensing operations. For example, data from Doppler instrumentation, related to the movement of fluids or other measure of the fetal environment can be relied upon to guide the drug delivery protocol.

[0145] One method for modulating the fetal environment in the treatment of a fetus uses a drug delivery system that is surgically implanted in the mother, and provides drug delivery directly a fetal target such as the umbilical cord, the placenta, or the amniotic fluid. Rather than being a system which utilizes sensors and active pumping means, the delivery system may simply be a drug eluting stent, which is positioned, for example, within an umbilical vessel or within the vasculature which feeds the maternal side of the placenta. While stents have been used to assist in maintaining arterial integrity after angioplasty, these have not been used to modify fluids moving towards the fetus, to deter umbilical cord complications such as bending, kinking or knotting, have not been implanted within an umbilical vessel or the placental vasculature, and have not been implanted in one patient (mother) to affect the medical condition of a second patient (fetus). Alternatively, a catheter from a constant flow, spring or gas powered implantable drug pump may be situated to deliver drug delivery to a fetal target area. For example, when using one or more drugs to therapeutically treat a fetal disorder by means of a drug delivery system, a catheter may have a proximal end which is coupled to the pump and a distal portion for infusing therapeutic dosages of the one or more drugs. The method of using this drug delivery system can entail surgically implanting the catheter so that the distal portion tends to release drug primarily to at least one target structure, which may be, for example, within the fetal compartment or the placental compartment; and, operating the delivery system to discharge a predetermined

dosage of the one or more drugs through the distal portion of the catheter into the infusion site, whereby the fetal disorder is thereby treated. The step of surgically implanting the catheter, comprises, for example, situating the distal end either adjacent to or within a predetermined infusion site, which is, for example, a target structure which is related to the disorder or a structure which terminates or supplies blood to such a target structure.

[0146] In another method of using an implantable drug delivery system for delivering fluid to an unborn fetus, the steps may include: the step of implanting drug delivery system into a pregnant woman; the step of coupling a delivery means for fluid communication with an umbilical artery of the umbilical cord; and, the step of using an attachment means to reversibly secure the delivery means for fluid communication with the umbilical cord. In many instances the delivery means may be the distal tip of a catheter, but this may also be a microchip drug delivery system or may be the delivery portion of a small osmotic pump which is situated in the region intended for drug delivery. If the drug delivery system, has active elements, and contains a catheter which can be used to permit fluid to flow into the drug delivery system, the treatment may also include inserting a influx means (e.g., the catheter) into at least one umbilical vessel (e.g. umbilical artery) of the umbilical cord for enabling fluids to enter, or be drawn, into the drug delivery system. Treatment can also comprise the steps of; filtering these fluids in order to remove an unwanted substance; and, the step of sending the filtered fluid back into at least one umbilical vessel (e.g., artery). When filtering is used, the step of periodically purging said drug delivery system of said filtered unwanted substance, may also occur. For example, the step of operating said system in a purging mode can send any unwanted substance through a certain catheter, so that said unwanted material does not re-enter an area where it can affect the fetus. In one embodiment, the filtrate is purged in a manner that enables medical personnel to collect this filtrate for external analysis. When the method of using an implantable drug pump to provide medical treatment to a fetus includes removing a substance which is harmful to a fetus, the removal of said substance may occur though controlled shunting of the substance to a distal location. In one example, the substance which is harmful can be a heavy metal and the disorder for which treatment is being provided is autism. Heavy metal toxicity has been associated with number of neurological disorders, and while delivering such antioxidants as Ebselen may be one method of decreasing the risk of these disorders in the fetus, this type of prophylactic drug delivery may be done in conjunction with the removal of trace amounts unwanted filtrates, such as heavy metals.

[0147] In another method of treating a fetus with drug delivery, where sensing is utilized to guide treatment using the drug delivery system, a first step of sensing data related to said fetal disorder occurs either continuously, periodically, or according to a sensing schedule which may be modified based upon the recent history of the fetus (e.g., including data sensed over a recent period such as the last 2 hours), and which may be contained in a memory or database of the drug delivery system. For example, if data from an EMG sensor indicates that average fetal movement over a recent period of measurement has decreased considerably from that measured in a prior period (i.e., a recent self-norm), then blood oxygen may be sensed to determine if a hypoxic event is occurring. During a 2nd step, which comprises evaluation of sensed data, any data which is sensed can be evaluated to determine if a positive or negative event has occurred. In the case of a positive event drug delivery occurs according to the current delivery protocol. A 3rd step of operating the deliver system includes the step of controlling the operation of the pump, in response to the step of evaluating the sensed data, and delivering drug (e.g., via a predetermined dosage, or dosage based upon sensed data) of the one or more drugs when the evaluation of the sensed data produces a positive result.

[0148] In another embodiment of a method for treating fetal disorders by means of a drug delivery system, delivery occurs by means of one or more catheters, each having a proximal end functionally coupled accept drug pumped by the delivery system, and a distal portion, comprised of at least one lumen, which is placed appropriately for drug delivery to occur at, in, or proximate to, a targeted anatomical site. In this method, the steps may include: the step of implanting at least one lumen so that the distal portion lies in direct communication with a portion of tissue of a target structure, such as a structure in the fetal compartment, the placental compartment, or the amniotic sac; the step of coupling the proximal end of the at least one implanted catheter to the drug pump; and operating the drug pump to delivery drug the target structure. If sensors are used by the drug delivery system then the treatment can also include the steps of sensing the extent of the fetal disorder and using this to determine a drug delivery protocol; and controlling the operation of the drug delivery according to the delivery protocol. The step of controlling can comprise the step of executing a control algorithm which utilizes the sensed data to provide drug delivery function that determines, drug type, rate and dose. The step of controlling may also include the step of adjusting at least one parameter of the drug delivery protocol, the parameter being selected from the group consisting of drug, volume, concentration, flow rate, and pattern of delivery.

[0149] In one method of using an implantable drug delivery system, for delivering drug to an unborn fetus, includes the steps of: using sensors to obtain sensed data; the step of evaluating said sensed data in order to obtain a positive or negative result; and in the case of a positive result, the step of delivering at least one drug. The sensors may sense data pertaining to at least the amniotic fluid, or fluid transported within the umbilical vein, or umbilical artery, or maternal blood, or sense data pertaining to at least maternal EKG, fetal EKG, fetal EEG, or intrauterine pressure. The sensors sense may sense such measures as chemical composition, or infrared/red reflectance which can be used to determine oxygen saturation, or electric field potentials, or pressure. The step of performing an evaluation of sensed data may include comparing one or more values of the sensed data to normative data which may be a self-norm (e.g., including data from a previous time or set of times) or an age or sex appropriate population norm. The outcome of said evaluation can be determined by comparing the sensed data to this normative data using one or more threshold or statistical criteria. For example, the sensed data for some measure must exceed 2 standard deviations of a self-norm for that measure for a positive result to occur. Further, the step of performing an evaluation of sensed data can include using the values of the sensed data from two sensors (e.g., from a sensor which senses data from the umbilical vein and from

a sensor which senses data from the umbilical arteries) in order to compute an input/output function for at least one sensed substance. Additionally this step can include comparing this input/output function to normative data which may be a self norm from a previous time or set of times or an age and sex appropriate population norm. Again, the outcome of this evaluation (e.g. a positive or negative result) can be determined by one ore more threshold or a statistical criteria.

[0150] In another method of using an implantable drug pump to provide medical treatment to a fetus, the treatment includes: the step of implanting one or more sensors in one or more locations, for example, the fetal compartment, the maternal compartment, the womb, the amniotic fluid, the placenta, the maternal side of the placenta, the fetal side of the placenta, the arterial or venous passageways of the umbilical cord, the chorion plate, or the uterus; which is followed by the step of periodically sensing data from one or more sensors to generate sensed data and processing the sensed data to produce processed data, and the step of evaluating this processed data, using an evaluation routine which produces either a positive result, wherein drug delivery occurs according to a drug delivery protocol, or a negative result, wherein drug delivery does not occur. The evaluation routine may entail relying upon simple threshold criteria or complex statistical or modeling criteria, and this routine can be realized using the computer means of the drug delivery system and its various software **320** modules as well as values from a database. Alternatively, as discussed, the drug delivery system can simply be a drug eluting stent, which may consist of several layers of drug coatings which deliver drug differently, or which deliver different drugs, at different times of the pregnancy.

[0151] In any case, regardless of whether a simple or complex drug delivery system is used (or even if several drug delivery systems are used), the modification of the fetal environment, which can include modification of the fluids provided to the fetus, can be used to treat many disorders. The medical treatment comprises a drug treatment protocol that can be designed to increase the chance of achieving many types of therapeutic effects, such as, for example, improving the nutritional content of fluids flowing to the fetus; treating a disorder of the placenta (e.g., an anatomical, a biochemical, metabolic or a transport disorder); treating a hypoxic disorder, a metabolic disorder, a genetic disorder, physiological disorder, hormonal disorder, or an anatomic disorder of the fetus; treating a metabolic disorder, genetic disorder, nutritional disorder, physiological disorder, hormonal disorder, and anatomic disorder, of the mother, said treatment being modified with respect to the health of the fetus; providing gene-based therapy, compensating for substances to which the fetus is exposed due to a drug to which the mother is exposed; reducing the risk of preterm labor; treating fetal insufficiency; reducing the likelihood of, or in the treatment of infections and bacterial growth; reducing the effects of toxins, and other harmful substances; reducing the effects of at least one substance that has at least one harmful effect on the fetus when said substance is present above a specific level; reducing the effects of a substance that has one or more harmful effects on the fetus when this substance fluctuates beyond a specified level over a specified amount of time. The medical treatment can rely upon a drug delivery protocol that is modified based upon at least one characteristic of the fetus, for example, gestational age, fetal metabolic level, metabolites produced by the fetus, fetal weight, fetal head circumference, the volume of an anatomic structure of the fetus. In one embodiment, the method of using the drug delivery system comprises delivering drug to a maternal afferent structure and occurs when an evaluation routine, which compares sensed data to normative data of a database, produces a positive result.

[0152] When the method of using a drug delivery system involves treatment which provides a drug that causes a chemical or molecular transformation, in at least one substance that would normally produce a harmful effect on the fetus, the harmful effect of this substance is decreased. For example, the harmful substances which are treated by the therapy can be carbon dioxide, bicarbonate, lactic acid, or an excess of hydrogen ions and the harmful effect is acidosis.

[0153] A main advantage of certain embodiments of the current methods and systems of drug delivery are that, the state/condition of both the mother and fetus are considered in terms of the effects of drug delivery. For example, the drug treatment of a mother (or fetus) may be modified due to changes sensed in the fetus (or mother). Alternatively, rather than modifying the treatment intended for the mother, the originally intended treatment can be accomplished, unaltered, while compensatory drugs are delivered to the fetus, or to a structure such as the placenta, in order to compensate for the unwanted effects that occur due to the treatment of the mother. In one example, a method of using the implantable DDS for delivering one or more drugs to provide medical treatment to a mother comprises the steps of modifying the drug delivery regimen based upon, for example, data relating to prior drug delivery and its effects on the fetus or a knowledge of its potential effects on the fetus, sensed data relating to the infant, or sensed data relating to both the mother and fetus. When a modification, of the delivery protocols for one or more drugs which are to provide medical treatment to a mother, occurs, this modification can comprise limiting the total amount of drug delivered with respect to a specified amount of time. Alternatively, this modification may comprise delivering a second drug to the mother or the fetus which will attenuate any unwanted effects of the first drug. In another example, a method of using the implantable DDS for delivering one or more drugs to provide medical treatment to a fetus comprises the steps of modifying the drug delivery regimen, for example, data relating to prior drug delivery and its effects on the fetus or a knowledge of its potential effects on the fetus, sensed data relating to the infant, or sensed data relating to both the mother and infant. When a modification, of the delivery protocols, for one or more drugs which are to provide medical treatment to a fetus, occurs, this modification can comprise limiting the total amount of drug delivered with respect to a specified amount of time. Alternatively, this modification may comprise delivering a second drug. The modification of drug delivery in both these examples can be determined, in part, by data stored in a database that contains upper limits which are based upon an equation or model whose variables represent characteristics of the fetus, for example, predicted gestational age, head volume, body volume or at least one of the following for at least the fetus or the mother: body weight estimate, absolute or relative levels of current or past sensed data, or changes in the levels of sensed data, or a combination of the two, the sensed data relating to measures of metabolic rate, metabolites, chemical or biochemical substances, or physiological events.

[0154] In line with the strategy of providing a medical treatment that considers both the pregnant mother and the fetus, the drug delivery can occur for two patients. In one embodiment of a drug delivery method that delivers one or more drugs to provide medical treatment to a patient#1, there is a modification of the drug delivery regimen based upon at least data relating to prior drug delivery, data relating to the patient #2, or based upon data relating to both patient #1 and patient #2. In one example, patient #1 is a mother and patient #2 is a fetus and modification comprises, for example, limiting the total amount of drug delivered with respect to a specified amount of time or the modification comprises delivering a second drug. In another example, patient #1 is a fetus and patient #2 is a mother and the modification of the drug delivery regimen comprises, for example, limiting the total amount of drug delivered with respect to a specified amount of time.

[0155] The method for treating fetal disorders using a drug delivery system may simply comprise the steps of scheduling a drug delivery event; awaiting the drug delivery event; and, delivering drug delivery event representative of the treatment protocol that is chosen to treat a fetal disorder, wherein the steps of scheduling, awaiting, and delivering are repeated periodically or continuously. Alternatively, if sensing is used, then a method for treating a fetal disorder with a drug delivery device can occur wherein drug delivery is adaptive to a characteristic of a sensed signal (e.g., a signal sensed from the fetal, maternal, or placental compartments) said method comprising the steps of: measuring the characteristic of the sensed signal; generating a drug delivery treatment protocol from the characteristic; and delivering drug therapy representative of the drug delivery treatment protocol. Delivery may occur only when evaluation of the sensed signal produces a positive result, and if this occurs, then the sensed signal is also used to determine the characteristics of the delivery. A positive result can occur when a medical event is detected in the sensed signal, for example, when measuring a characteristic (i.e., evaluation of sensed data from a specified number of EMG sensors) indicate that activity levels have been above a certain amount and within a certain frequency range for a given amount of time, then the medical event may be pre-mature labor contractions, and drug is dispensed to treat this event. The step of measuring a characteristic of the sensed signal can comprise the steps of processing the sensed data using signal processing to obtain processed data; then transforming the processed data so that it reflects a relevant characteristic of the data in meaningful units, and then evaluating the processed data to obtain a measurement of the characteristic. Transformations of the sensed data can produce, for example, estimates of magnitude, concentration, or duration. In one embodiment, the step of generating a drug delivery treatment protocol comprises the steps of selecting a drug delivery treatment protocol from a database and performing drug delivery according to the drug delivery treatment protocol.

[0156] In an alternative method of delivering one or more drugs to therapeutically treat a fetal disorder, a device capable of storing and releasing the one or more drugs in at least one target structure (e.g., the fetal compartment or the placental compartment), is surgically implanted so that the one or more drugs may be released in or near a target structure and the method comprises the steps of; providing a drug delivery system with at least one catheter having a proximal end and a distal end, the proximal end of the catheter coupled to the drug delivery system; surgically implanting the catheter of said system so that the distal end may deliver drug to a site chosen to be relevant to the fetal disorder; operating the drug delivery system to deliver drug to the chosen target structure; and, treating a fetal disorder with the drug that may be released into the target structure. Additionally, the drug delivery system can sense data related to the fetal disorder; and the step of operating the drug delivery system includes the step of dispensing drug in response to the step of sensing data, whereby the drug delivery is regulated in accordance with evaluation of a characteristic of the sensed data. When sensed data is to be obtained, the sensor can also be surgically implanted or may exist externally to the patient.

[0157] While the methods of treating a fetus using drug delivery can use many types of drug delivery systems, the apparatus for providing drug delivery can have sensors for sensing relevant data from at least the amniotic fluid, umbilical vein, umbilical artery, maternal blood, or for sensing maternal EKG, fetal EKG, or fetal EEG. In one embodiment of a drug delivery system for modulating the fetal environment is an implantable drug delivery system that contains a drug selected to treat a pregnant female for a specific medical condition which is relevant to the fetus. For example, the drug can be selected to be one of the following: tocolytics, oxytocin antagonists, cyclo-oxygenase inhibitors, calcium channel blockers, selenium, and beta2 agonists. Additionally, the drug delivery system, when configured for delivering drugs into the fetal compartment, may provide a rate drug delivery or dose which is approximately 5-50% that provided by drug delivery systems configured for adults, at least in the earlier stages of pregnancy. Further, the drug delivery system can contain at least one drug delivery protocol, which may be stored in a database of protocols, which is specifically configured to treat or deter a fetal disorder.

[0158] Various components of the medical drug delivery system can be miniaturized considerably compared to the embodiments shown in the FIGs. The scale of components in the FIGs are for illustration purposes and do not necessarily represent the sizes and scales of the components.

[0159] Components of the drug delivery system can be external, for example, attached to the arm placement with the catheters passing subcutaneously.

[0160] Although the disclosure herein has been drawn to one or more exemplary systems and methods for drug delivery devices, various modifications thereof will be apparent to those skilled in the art without departing from the spirit and scope of the invention as outlined in the claims appended hereto.

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What is claimed is:

1. A method using a drug delivery system for modulating the fetal environment, said method comprising:

a. sensing data from at least one sensor configured to provide sensed data from at least one of the following: a pregnant female and a fetus,

b. evaluating said sensed data to obtain a positive or negative result, and

c. in the case of a positive result operating a drug delivery system according to a drug delivery protocol to cause drug delivery.

2. The method of claim 1 wherein said positive result determines which of at least two drug delivery protocols is used to accomplish drug delivery.

3. The method of claim 1 wherein said positive result serves as a control signal which controls drug delivery.

4. The method of claim 1 wherein said positive result occurs when a medical event is detected.

5. The method of claim 1 wherein evaluating said data to obtain a positive or negative result comprises comparing sensed data to at least one of the following comparison measures: a self norm, population norm, an absolute value, percentage value, a value calculated from a ratio, multivariate equation, and a model.

6. The comparison measures of claim 1 wherein any of the comparison measures are derived in relation to at least one of the following: age, gestational age, physical characteristics including fetal head or abdominal circumference, or body volume, maternal or fetal weight, and predicted age.

7. The method of claim 1 wherein said at least one sensor includes at least one of: a biosensor, a chemical sensor, an optical sensor, an electrode for sensing ECG and EEG signals, a PH sensor, a gas sensor, a flow sensor, and a pressure sensor.

8. The method of claim 1 wherein said drug delivery consists of delivering at least one of the following: blood thinning agents, anticoagulants.

9. The method of claim 1 wherein said drug delivery consists of delivering drugs to at least one of the following: a vessel in the umbilical cord, an umbilical vein, the placenta, the womb, the amniotic fluid, the maternal side of the placenta, the fetal side of the placenta, the arterial passageways of the umbilical cord, the chorion plate, the placenta, and the uterus.

10. The method of claim 1 wherein said sensors sense data from at least one of the following: a vessel in the umbilical cord, an umbilical vein, the placenta, the womb, the amniotic fluid, the maternal side of the placenta, the fetal side of the placenta, the arterial passageways of the umbilical cord, the chorion plate, the placenta, and the uterus.

11. The method of claim 1 wherein said drug delivery system periodically operates in a sample-push mode in order to provide samples to medical personal.

12. A method of using the drug delivery system of claim 1 wherein modulating the fetal environment decreases the risk of pre-term labor and drug delivery delivers at least on of the following: tocolytics, oxytocin antagonists, cyclo-oxygenase inhibitors, calcium channel blockers, and beta2 agonists.

13. A method of claim 1 wherein modulating the fetal environment decreases the incidence of intrauterine infection and abnormal bacterial levels.

14. The method of claim 1 in which the at least one sensor is configured to sense at least one of the following: interleukin-6 or fibronectin in cervical secretions and in amniotic fluid, C-reactive protein level of the maternal venous blood, and the said drug delivery is an antibiotic.

15. The method of claim 1 wherein modulating the fetal environment augments the immune system of the fetus, and wherein drug delivery comprises delivering selenium.

16. A method for modulating the fetal environment using a drug delivery system, said method comprising implanting a drug delivery system to provide drug delivery directly to at least one of the following: the umbilical cord, the placenta, the amniotic fluid.

17. The method of claim 16, wherein the drug delivery system is at least one of the following: at coated stent, a constant flow implantable drug pump.

18. The method for treating a fetal disorder of claim 1, wherein the step of delivering drug therapy comprises the steps of:

scheduling a drug delivery event;

awaiting the drug delivery event; and

delivering drug delivery even representative of the treatment protocol.

19. The method of claims **1** and **16** wherein the modulating of the fetal environment comprises using a drug treatment protocol designed to achieve at least one of the following

a. improve the nutritional content of fluids flowing to the fetus

b. treat a disorder of the placenta

c. treat at least one of: a hypoxic disorder, a metabolic disorder, a genetic disorder, physiological disorder, hormonal disorder, and an anatomic disorder of the fetus

d. treat at least one of: a metabolic disorder, genetic disorder, nutritional disorder, physiological disorder, hormonal disorder, and anatomic disorder, of the mother

e. compensate for substances to which the fetus is exposed due to a drug to which the mother is exposed

f. reduce the risk of preterm labor

g. treat fetal insufficiency

h. reduce the likelihood of, or in the treatment of infections and bacterial growth.

i. reduce the effects of toxins, and other harmful substances

j. reduce the effects of at least one substance that has at least one harmful effect on the fetus when said substance is present above a specific level

k. reduce the effects of at least one substance that has at least one harmful effect on the fetus when said substance fluctuates over a specified amount of time beyond a specified level.

20. The methods of claim 1 and 16 wherein drug delivery constitutes delivering a drug which causes a chemical or molecular transformation in at least one substance that produces a harmful effect on the fetus so that the harmful effect of this substance is decreased.

21. The method of claim 20, where the substance is carbon dioxide, bicarbonate, lactic acid, and hydrogen ions and the harmful effect is acidosis.

22. The disorders of the placenta of claim 19, wherein the disorder is chosen from at least one of the following: an anatomical, a biochemical, metabolic, or a transport disorder.

23. The method of claim 19 wherein the drug delivery protocol is based upon at least one characteristic of the fetus, said characteristic chosen from the following: gestational age, fetal metabolic level, metabolites produced by the fetus, fetal weight, fetal head circumference, and the volume of an anatomic structure of the fetus.

24. A method of using an implantable drug delivery system to deliver one or more drugs to provide medical treatment to a patient#1 which comprises a modification of the drug delivery regimen based upon data relating to at least one of the following: data relating to prior drug delivery, data relating to the patient #1, data relating to the patient #2, and data relating to both patient #1 and patient #2.

25. A method of using the implantable DDS for delivering one or more drugs to provide medical treatment to patient #1 claim 24, wherein said patient #1 is a mother and patient #2 is a fetus and modification comprises limiting the total amount of drug delivered with respect to a specified amount of time.

26. A method of using the implantable DDS for delivering one or more drugs to provide medical treatment to patient #1 claim 24, wherein said patient #1 is the mother and patient #2 is a fetus and said modification comprises delivering a second drug.

27. A method of using the implantable DDS for delivering one or more drugs to provide medical treatment to patient #1 claim 24, wherein said patient #1 is a fetus and patient #2 is a mother and modification comprises limiting the total amount of drug delivered with respect to a specified amount of time.

28. A method of using an implantable drug pump to provide medical treatment to a fetus which includes removing a substance which is harmful to a fetus by at least one of the following: controlled shunting of said substance to a distal location, filtration, dispensing a drug which will chemically affect said harmful substance to provide therapeutic relief.

29. The method of claim 28 wherein the substance which is harmful is a heavy metal and the disorder is autism.

30. A drug delivery system, for modulating the fetal environment comprising an implantable drug delivery system containing a drug selected to treat a specific medical condition in a pregnant female.

31. The drug delivery system of claim 30, wherein said drug is selected to be at least one of the following: tocolytics, oxytocin antagonists, cyclo-oxygenase inhibitors, calcium channel blockers, selenium, and beta2 agonists.

32. The drug delivery system of claim 30, wherein, said implantable drug delivery system provides a rate of drug delivery which is approximately 5-50% that provided by drug delivery systems configured for adults.

33. The drug delivery system of claim 30, which also includes a database of at least one drug delivery protocol configured to treat or deter the harmful affects of a fetal disorder.

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