Feasibility of intracranial surgery in the primate fetus

Model and surgical principles

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A research model for intracranial surgery in the primate fetus was developed and tested in 10 timed-pregnant rhesus monkeys. With general anesthesia and sterile surgical technique, a laparotomy followed by a lower uterine segment hysterotomy was performed at a site avoiding the placenta. The amnion was opened carefully by use of the operative microscope and the fetal head was exposed. A scalp incision was made over the frontal region and a small craniectomy and cortical incision were carried out. In three of the fetuses, ventricular shunts were also placed. A layered closure was performed and the uterus was returned to the peritoneal cavity. Placental integrity and fetal viability were assessed before surgery and 1 week postoperatively by ultrasonography. The survival rates were 100% for the mothers and 80% for the fetuses. One fetus died in utero after an overdose of a sedative to the mother, and another was stillborn. Postmortem examination revealed no intracranial or systemic abnormalities in either case, and the cause of death was attributed to drug overdose and a naturally occurring stillbirth, respectively. Newborns were maintained either with their mothers or in a nursery, where they were observed and evaluated for 3 weeks. Weight, crown-rump length, and occipitofrontal head circumference were measured. General patterns of behavior and neurological assessments were recorded weekly. The eight surviving neonates were normal with respect to all parameters evaluated. Several principles of fetal intracranial surgery are emphasized as important: uterine relaxation by prostaglandin inhibition; low-dose halothane anesthesia supplemented by nitrous oxide in oxygen; perioperative ultrasonography and intraoperative transillumination of the uterus for placental localization; lower uterine segment opening; controlled exposure of the fetal cranium; minimization of amniotic fluid loss; enhancement of fetal anesthesia by injection of a local anesthetic agent at the fetal operative site; and multilayered watertight closure.

KEY WORDS • intrauterine intracranial surgery • fetal surgery • primate model • rhesus monkey

RECENT advances in antenatal diagnostic techniques have enabled the identification of many fetal diseases and malformations, and have prompted the investigation of potentially corrective therapy in utero. However, attempts to treat fetal abnormalities have yielded variable results. Before such procedures can be performed safely upon the human fetus, they should be developed and thoroughly tested in a primate model under laboratory conditions.

Physiological studies of the monkey fetus requiring monitoring techniques have been conducted effectively, but direct fetal intervention in the primate has not previously met with a great degree of success. We report here a research model for intracranial surgery in the primate fetus that we developed while studying congenital hydrocephalus. Techniques for the performance of a fetal craniotomy in the primate are described, and the principles of fetal surgery are discussed.

Materials and Methods

Subjects

Ten timed-pregnant rhesus monkeys (Macaca mulatta), all multiparous breeders weighing between 4 and 8 kg each, were used in the study. The females had been mated for 48 hours and were tested for pregnancy 2 weeks thereafter. A confirmed pregnancy was timed by back-dating to the mating period.

Preparation, Monitoring, and Anesthesia

Surgery was performed between the 120th and 130th day of pregnancy (term is between 160 and 165 days).
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Three to 5 days prior to surgery, a fetal ultrasonogram was obtained. The mother was fasted after midnight on the day of surgery. Preoperative sedation was achieved by an intramuscular injection (3 mg/kg) of an acepromazine-ketamine mixture (1.66% acepromazine maleate and 98.34% Ketaset). Subcutaneous atropine sulfate (0.2 mg/kg) was administered and a single dose of nafcillin (125 mg) was injected intramuscularly. An intravenous catheter was placed into the antecubital fossa for continuous intraoperative administration of 5% dextrose in a 0.45% saline solution. The first two monkeys in the study were treated with diazoxide (Hyperstat, 30 mg), a smooth-muscle relaxant, to inhibit uterine contractions. This was given intravenously at the time of the skin incision and at 30-minute intervals during the procedure. A prostaglandin inhibitor, indomethacin (Indocin, 10 mg), was given intravenously to the remaining eight monkeys 1 hour prior to surgery and 2 hours after the skin incision in order to promote uterine relaxation. The mother's blood pressure was recorded with a neonatal sphygmomanometer and Doppler ultrasonograph* over the brachial artery. Maternal temperature was monitored by a rectal probe and body temperature was maintained at 37.5°C with a thermo-blanket. Precordial leads were secured subcutaneously for continuous recording of heart rate and respiration. Endotracheal intubation (cuffed) was performed and the animal was anesthetized with halothane (Fluothane, 0.125% to 0.25%) and 50% nitrous oxide in oxygen. Respiration was controlled by the anesthetist.

Surgical Technique

Sterile techniques were used for surgery. With the animal positioned supine on the operating table, the abdomen was prepared with a povidone-iodine solution (EZ Scrub) and draped. During the initial phase of the procedure, a fiberoptic headlight and loupes (magnifying × 4.5) were used. A midline incision was made below the umbilicus, and the abdominal muscles were split in the direction of their fibers. After the peritoneum was opened, the uterus was partially delivered from the abdominal cavity and covered with moist gauze sponges to prevent drying. The position of the placenta was outlined by transilluminating the uterine wall with a coaxial light, and was correlated with the preoperative ultrasonogram. The fetal parts were located by palpation, and the uterine incision was made at a site avoiding the placenta in the lower uterine segment (Fig. 1A). Exposure of the fetal head was maximized by gently maneuvering it beneath the incision. The headlight and magnifying loupe were then removed, and the procedure was continued under an operating microscope at magnification of × 10 to × 25.

The fetal cranium was maintained at the uterine opening against the amnion in order to open it with little or no loss of fluid (Fig. 1B). The amnion was carefully incised without fragmentation and the fetal head was partially exteriorized (Fig. 2A). A scalp incision was made over the frontal region, and a small craniectomy was performed using a microrongeur (Fig. 2B). The dura was opened with fine iridectomy scissors exposing the underlying cortical surface (Fig. 2B). Microbipolar forceps were used to coagulate the fetal arachnoid which was then opened with a microknife. The cerebral cortex was incised and a 2-cm corticotomy of approximately 7 to 8 mm in depth was performed. In three of the fetuses, a prototype of a fetal shunt with a low-pressure distal-slit valve developed in our laboratory† was placed through the cortical incision into the frontal horn of the lateral ventricle with resultant egress of cerebrospinal fluid. In one fetus the distal end of the shunt was placed in the subgaleal space, and in the other two it was tunneled subcutaneously beneath the scalp and passed through a separate stab wound incision to rest within the amniotic cavity. Hemostasis was achieved by use of bipolar electrocoagulation. The scalp was then closed with interrupted 5-0 nylon sutures (Fig. 3A), and the amnion was approximated in watertight

* Doppler ultrasonograph manufactured by Parks Electronic Laboratory, Beaverton, Oregon.

Fashion with continuous 7-0 nylon sutures (Fig. 3B). A double-layer closure was given to the uterine wall and the uterus was returned to the peritoneal cavity (Fig. 3C). The abdominal musculature and fascia were sutured in separate layers with 2-0 chromic catgut, and the skin was approximated by 4-0 nylon sutures.

The animal was allowed to recover in a quiet area and was then returned to the monkey colony. The progress of the pregnancy was assessed 1 week after surgery by ultrasonography under ketamine sedation.

Delivery

A natural vaginal delivery was allowed unless there was need for a Caesarean section. The weight and crown-rump length of the newborn were recorded at birth and complete neonatal physical and neurological examinations were performed. The newborns were maintained either with their mothers or in a nursery if the mother did not accept the baby.

Postnatal Management

All newborn animals were observed and evaluated for 3 weeks. Weight, crown-rump length, and occipitofrontal head circumference were measured. General patterns of behavior including sociability, feeding habits, and newborn-maternal interaction were recorded weekly for 3 weeks, along with other general observations.

Neurological assessments performed weekly for 3 weeks on all animals included examination of eye movements (elevation, depression, adduction, and abduction); bulbar function (sucking and swallowing); gait ability; and deep-tendon reflexes. Gait was evaluated according to the following scale: 0 = no voluntary movement; 1 = perceptible movement of the joints; 2 = good movement at the joints but inability to stand; 3 = ability to stand and walk one or two steps; 4 = ability to walk several steps, although unsteady; and 5 = normal gait. The deep-tendon reflexes were assessed as follows: 0 = absent; 1 = hypoactive; 2 = normal; 3 = hyperactive; and 4 = hyperactive with clonus.

Sonographic Examination

Ultrasound examination of the fetus was performed 3 to 5 days before in utero surgery and 1 week postoperatively. This examination comprised assessment of placental integrity, fetal viability, and the cranial surgical site.
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**TABLE 1**

Intracranial surgery in the fetus of 10 rhesus monkeys

<table>
<thead>
<tr>
<th>Maternal No.</th>
<th>Maternal Age (yrs)</th>
<th>Maternal Wt (kg)</th>
<th>Fetal Age At Surgery (days)</th>
<th>Uterine Relaxant</th>
<th>Anesthesia*</th>
<th>Fetal Procedure</th>
<th>Delivery Method &amp; Fetal Age</th>
<th>Newborn Status &amp; Weight</th>
<th>Clinical Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>8.75</td>
<td>130</td>
<td>Craniotomy &amp; placement of ventriculosubgaleal shunt</td>
<td>Caesarean section, 166 days</td>
<td></td>
<td></td>
<td>stillborn</td>
<td>postmortem: shunt in place; brain autolyzed; no abnormalities</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>122</td>
<td>Craniotomy &amp; cortical incision</td>
<td>vaginal, 152 days</td>
<td>viable, 14.2 oz</td>
<td></td>
<td>normal neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>125</td>
<td>Craniotomy &amp; cortical incision</td>
<td>vaginal, 148 days</td>
<td>viable, 15.4 oz</td>
<td></td>
<td>normal neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>127</td>
<td>Craniotomy &amp; placement of ventriculoamniotic shunt</td>
<td>vaginal, 153 days</td>
<td>stillborn</td>
<td></td>
<td>postmortem: lungs collapsed; otherwise normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>124</td>
<td>Craniotomy &amp; cortical incision</td>
<td>vaginal, 148 days</td>
<td>viable, 15.75 oz</td>
<td></td>
<td>normal neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>120</td>
<td>Craniotomy &amp; cortical incision</td>
<td>vaginal, 155 days</td>
<td>viable, 14.6 oz</td>
<td></td>
<td>normal neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>128</td>
<td>Craniotomy &amp; cortical incision</td>
<td>vaginal, 148 days</td>
<td>viable, 15.8 oz</td>
<td></td>
<td>normal neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>121</td>
<td>Craniotomy &amp; cortical incision</td>
<td>vaginal, 145 days</td>
<td>viable, 14.8 oz</td>
<td></td>
<td>normal neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>120</td>
<td>Craniotomy &amp; cortical incision</td>
<td>vaginal, 160 days</td>
<td>viable, 13.7 oz</td>
<td></td>
<td>normal neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>120</td>
<td>Craniotomy &amp; cortical incision</td>
<td>Caesarean section, 163 days</td>
<td>viable, 15 oz</td>
<td></td>
<td>normal neonate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Nembutal = pentobarbital; Flaxedil = gallamine triethiodide.

**Results**

Maternal survival rate was 100%. Eight of the 10 fetuses that underwent intracranial surgery survived (Table 1).

A ventriculosubgaleal shunt had been placed in one of the fetuses that did not survive. Viability was confirmed on the 3rd postoperative day by ultrasonography. Two days later, with the mother sedated by pentobarbital (Nembutal), an abdominal computerized tomography scan was obtained (Fig. 4); however, an overdose of Nembutal was inadvertently administered to the mother during scanning, and this resulted in slowed, shallow respiration and a marked drop in blood pressure. Resuscitation efforts were successful but the fetus was adversely affected. An ultrasonogram 1 week later confirmed fetal death. Because the dead fetus was not expelled, a Caesarean section was performed. Postmortem examination demonstrated the shunt to be adequately placed with no associated intracranial complications and no systemic abnormalities. It was concluded that the death of this fetus was secondary to the Nembutal overdose.

The other fetus not to survive had undergone craniotomy, corticotomy, and placement of a ventriculoamniotic shunt. Ultrasonographic examination performed 1 week after surgery confirmed fetal viability. Pregnancy

**Fig. 4.** Computerized tomography scan of a rhesus monkey fetus following placement of a fetal shunt. FC: fetal cranium; S: radiopaque tip of the ventricular catheter; AC: amniotic cavity; V: maternal vertebral body. (Reproduced from Brodner RA: Antenatal diagnosis and treatment of hydrocephalus, in Wilkins RH, Rengachary SS (eds): Neurosurgery. New York: McGraw-Hill, 1985, Vol 3, p 2158, with permission.)
progressed uneventfully; however, the fetus was stillborn. A postmortem examination revealed good shunt placement with no significant intracranial or systemic findings except for signs of early healing at the site of cerebral incision. This fetal death was considered to represent the natural late gestational and early neonatal mortality rate in rhesus monkeys which ranges over 20%.20,23,24

Only two Caesarean sections were done in this study; one for a dead fetus and another for an overdue delivery. Vaginal deliveries of the eight other animals were uneventful. No abnormalities were noted among the newborns relative to their physical and neurological examinations. Initial gait testing in the 1-week-old infant was difficult, but by 3 weeks of age all neonates demonstrated the ability to walk several steps. Outcome did not appear to be significantly affected by maternal or gestational age at surgery, duration of the procedure, or side of the fetal brain incised.

Discussion

The primate model of fetal intracranial surgery described here yielded fetal and maternal mortality rates comparable with those occurring naturally in the monkey. Eight of 10 fetuses undergoing craniotomy were viable at delivery and remained normal during the postnatal period of observation. One of the two fetuses that did not survive died in utero after a Nembutal overdose was inadvertently given to the mother. The other fetus was stillborn but had a normal postmortem examination and most likely represented the spontaneous fetal loss rate seen in the rhesus monkey.

Three of the fetuses in this study underwent in utero shunt placement; in one a ventriculosubgaleal shunt was placed and in two ventriculoamniotic shunts were used (Table 1). Both deaths occurred in shunted fetuses; however, one of these (Monkey 1) most likely died from a Nembutal overdose as previously discussed. The other (Monkey 4) was stillborn with a normal postmortem examination; the cause of death was unexplained. Therefore, the variable of shunt placement may not have been a prominent factor in either fetal death.

Although survival following fetal surgery is readily achieved in sheep, it is much more difficult in primates because of the onset of premature labor.6,11,12,18,19,21 The uterine musculature in sheep is thin and does not contract as strongly as in the primate.6,11 Since the primate uterus has a greater reactivity, preterm labor and abortion are often precipitated by surgical invasion. Therefore, fetal surgery in the primate has been associated with a high rate of mortality.10,11,16,21 Myers16 reported a mortality rate of 46% following carotid artery surgery in the fetal monkey. Harrison, et al.,11 reported an overall fetal mortality rate of 50% in a study involving in utero bladder surgery in monkeys; however, in their last group, they were able to decrease the mortality rate to 20%. Taub, et al.,21 performed craniotomies in nine fetal rhesus monkeys, and seven (78%) died in utero. Glick, et al.,10 placed a ventriculoamniotic shunt in eight fetal monkeys with kaolin-induced hydrocephalus, and four of them survived. Michejda and Hodgen14 achieved an 80% fetal survival rate in nonhuman primates following in utero placement of a screw-in Havit ventriculoamniotic shunt. This procedure, however, required minimal fetal exposure and no craniotomy.

Every fetus in our study underwent an extensive open-womb procedure involving exteriorization of the head, formal craniotomy, dural opening, cortical incision, and layered closure; the overall fetal loss was 20%. Some aspects of our model that may have enhanced the survival rate are discussed below.

The anesthetic protocol in this model consisted of halothane inhalation supplemented by nitrous oxide in oxygen. The concentration of halothane used here (0.125% to 0.25%) was significantly lower than that previously reported.11,15,18 The first author (R.A.B.) had performed a small pilot study titrating halothane dose against maternal blood pressure in the gravid rhesus monkey (unpublished data, 1984). A tendency toward rapid hypotension was noted with halothane concentrations between 0.5% and 1%. Because such hypotensive episodes can be detrimental to the fetus, they were avoided by using lower concentrations of the anesthetic agent. Our experience demonstrates that the relaxant effect of halothane upon the uterine myometrium is adequate at concentrations of less than 0.25%, and it is therefore not necessary to exceed this level.

Prostaglandin inhibitors such as indomethacin have been found to exert a relaxant effect upon the uterine myometrium.4,11,17,18 In this model, indomethacin was effective in helping to prevent contractions of the uterus and secondary abortion. Because of the duration of our procedure (1 to 3 hours), indomethacin was administered in multiple doses rather than in a single dose as recommended by others.11 It was given 1 hour prior to surgery and at 2-hourly intervals thereafter until completion of the procedure. On the other hand, diazoxide, which was administered to the first two monkeys in our series, was found to be unsatisfactory since the dose required to effectively inhibit uterine contractions also induced significant maternal hypotension which necessitated treatment with ephedrine and intravenous fluids.

The surgical procedure was performed with the mother in the supine position. Although some investigators assert that the lateral decubitus position lessens the tendency of the uterus to compress the inferior vena cava and cause a secondary decrease in cardiac output,4,11,17,18 our experience with both has led us to choose the supine position, which proved to be successful. However, it is recommended that an anesthesiologist be present during surgery to monitor vital signs, so that if the uterus is impinging upon the vena cava, a drop in maternal blood pressure will be noted and the uterine position can be changed to relieve this compression. We consider the lateral decubitus position to be less favorable because the amniotic fluid tends to leak from the amniotic cavity. With the mother supine, the fluid...
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pools away from the uterine opening and is preserved more easily. We also found it slightly awkward to use the surgical microscope when the uterus was on its side rather than supine.

Prophylactic antibiotics were used intraoperatively in this model, and strict sterile technique was maintained throughout the surgery. Since the fetus does not have a well-developed immune system, it may be more susceptible to infection. By using intraoperative antibiotics and sterile methods, the incidence of infectious complications may be lessened, as in this study where no infections occurred.

Compromise of the placenta is a significant morbidity/mortality factor in fetal surgery. The rhesus monkey has a bidiscoid placenta with anterior and posterior fundal implantation and bridging vessels. When opening the uterine wall, it is important to avoid the placental margins as well as the interplacental vessels. If the placenta is lacerated, retroplacental hemorrhage and secondary separation may occur. Such complications are minimized, however, by using preoperative ultrasonography of the placenta and intraoperative transillumination of the uterine wall.

We chose to make the uterine incision over the lower uterine segment because this portion of the uterus is least reactive. Although a full bladder may infringe upon the surgical field in this area, catheterization is never necessary and is better avoided, as it is difficult to catheterize a female monkey, and retrograde infection can be readily introduced. It is preferable to pack the bladder with moist sponges and gently reflect it from the field.

The fetal anatomical part to undergo surgery, which in this study was the frontal cranium, may be manually rotated to the site of uterine incision before the amnion is opened. This allows the surgeon to make a relatively small incision into the amnion, thereby reducing the risk that the entire fetus will extrude. Although a completely exteriorized fetus can be returned to the uterus, this event is traumatic and is frequently associated with fetal mortality. In smaller animal models the fetus may be removed from the uterus and placed in a warm saline bath during the procedure.2

The amnion must be opened carefully so that closure after fetal surgery may be watertight. Fragmentation of the amnion will make adequate closure virtually impossible. As the amnion is opened, the surgical assistant should occlude the opening with the fetal head. This creates a tamponading effect and minimizes the loss of amniotic fluid, which is vital for fetal homeostasis. Placement of the mother in the Trendelenburg position further helps to prevent fluid loss. The previous traumatic technique used by us and others, including withdrawing the amniotic fluid prior to opening the amnion, placing it in an incubator, and then re-injecting it into the amniotic cavity at the time of closure,6,11,12,18 is obviated by the method described above.

Another technique that has been used to stabilize the operative site and prevent amniotic fluid loss is “marsupialization” of the fetus, which entails suturing the fetal skin to the uterine wall.6,12,18 However, the first author (R.A.B.) has found this technique to be traumatic: the myometrium often bleeds, the amnion may strip away from the uterine wall, the uterus can contract and rip the sutures, the skin may avulse away from the fetal body with the resultant collection of a large subcutaneous hematoma, and the amniotic fluid frequently leaks because the marsupialization is not watertight. In addition, the placement of sutures into and tension upon the uterine wall serve as irritants that increase the possibility of uterine contraction and abortion.

The amnion should not be removed from the fetal nares and/or mouth during the exposure, otherwise the fetus may begin to respire and asphyxiation may occur. Also, the fetal eyes are often open and should be protected by the amniotic sac from blood and other debris.

The fetus is not always anesthetized to the deepest surgical level when an 0.125% to 0.25% concentration of halothane is used. Occasionally, the fetus appreciates pain and will move in response to noxious stimuli such as the scalp and dural incisions. When this occurs, we have injected the fetal scalp and dura with 1 to 2 cc of 1% Xylocaine (lidocaine) to relieve the pain and to minimize fetal movement during the remainder of the procedure.

Fetal intracranial surgery requires gentle, atraumatic microsurgical technique. Absolute hemostasis is essential, since the fetus cannot tolerate any blood loss, and must be maintained as each layer (the uterine wall, amnion, and fetal scalp) is opened. In this model, hemostasis was readily attained by use of bipolar electrocoagulation. The fetal craniotomy should begin at a suture line, usually the coronal suture, in order to gain access to the cranial edge. It is dangerous to place a burr hole because of the bone’s thinness. In addition, the fetus tends to “float” away from the drill bit.

All anatomical layers should be closed separately. However, it is not necessary to close the dura. In this model, the dura of the first two animals was closed, but because this appeared to be unnecessary and was time-consuming, the exercise was not continued. A craniectomy is performed rather than the elevation of a bone flap because the former is quicker and less traumatic. The bone does not need to be replaced since the fetal dura has a high osteogenic capability and the cranium is almost completely reconstituted by the time of delivery. The scalp is approximated in interrupted fashion, including several sutures that are placed deeply to incorporate the pericranium so that the subgaleal space is obliterated. If the subgaleal space is not restricted, a subgaleal hematoma may form, causing a significant amount of blood to be sequestered.

It is important to close the amnion to ensure retention of amniotic fluid. The uterine wall is closed in double layers. The deepest layer involves the endometrium and inner myometrium. The edges of the endometrium should be approximated neatly and inversion avoided since this may predispose to the development
of endometriosis and compromise future breeding. The superficial layer of uterine closure incorporates the outer myometrial tissues and the serosa. We have utilized multilayered closure of the uterus in all our canine and primate procedures and have never experienced a uterine rupture during subsequent vaginal delivery.

As the uterus is replaced into the abdominal cavity, particular attention should be paid to maternal blood pressure. If maternal hypotension occurs, the uterine position should be adjusted because compression of the inferior vena cava is likely.

Conclusions

This study demonstrates the feasibility of a technique for intracranial surgery in the primate fetus. This model was developed using principles learned during the past 3 years in over 200 fetal procedures performed in the rat, dog, guinea pig, and monkey. These general principles can be applied in other fetal animal models, and in surgical procedures performed upon other parts of the fetal anatomy. Although this model was primarily designed as a research tool to study congenital anomalies of the nervous system, it can also be used to investigate the efficacy and safety of new fetal therapies which must be established in the subhuman primate before they can be applied to the human fetus. Although preliminary reports have suggested that several in utero surgical procedures may be beneficial, extensive work in the laboratory is still required. A primate model is needed in order that these investigations be conducted in a paradigm that closely simulates human gestation. The successful model demonstrated in this report can readily serve as a paradigm for such clinically oriented studies.

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