**Antenatal corticosteroids**

**Table A: Location, institution, ethics, animals and numbers**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Location** | **Institution** | **Ethics statement** | **Animal** | **Number Mothers** | **Number neonates** | **Estimated total (mothers and neonates)** | **Foetuses discarded / unaccounted for** |
| 157 | Japan | St. Marianna University | Performed according to guidelines | Wistar rats | 6 | 48 | 54 | *Some foetuses (no. unknown) unaccounted for* |
| 158 | USA | Departments of Pediatrics, | Approved by animal use committees | Sheep | 96 | 104 | 200 |  |
| 159 | USA | Dept obstetrics and gynecology | No | New Zealand Albino rabbits | 23 | 207 | 230 |  |
| 160 | USA | John Hopkins University | No | Rhesus monkeys | 14 | 14 | 28 |  |
| 161 | Netherlands; Italy; USA | Depts. Pediatrics; Dept Internal Medicine | Procedures reviewed and performed according to guidelines | Baboons | 10 | 10 | 20 |  |
| 162 | USA | St. Louis University School of Medicine | No | New Zealand white rabbits | 41 | 369 | 410 |  |
| 163 | USA | UCLA school of medicine | No | New Zealand white rabbits | 10 | 93 | 103 |  |
| 164 | USA | Dept. Pediatrics; Regional Primate Research Center | No | Rhesus monkeys | 63 | 63 | 126 |  |
| 165 | USA | Yale University School of Medicine | No | New Zealand white rabbits | 14 | 131 | 145 |  |
| 166 | USA | Yale University School of Medicine | No | New Zealand white rabbits | 29 | 124 | 153 | *At least 142* |
| 167 | USA | Harbor-UCLA Medical Center | No | New Zealand white rabbits | 35 | 111 | 146 | *About 150* |
| 168 | USA | UCLA Medical Center | No | New Zealand white rabbits | 48 | 260 | 308 | *About 172* |
| 169 | USA | UCLA School of Medicine | No | Rabbits | 60 | 200 | 260 | *About 400* |
| 170 | USA; Australia | Harbor-UCLA Medical Center; Institute for Child Health Research | Procedures reviewed and approved by animal use committees | Sheep | 67 | 67 *(including 12 dead foetuses)* | 134 |  |
| 171 | Australia; USA | Children’s Hospital Medical Center; Dept Obstetrics; Division Clinical  Sciences | Approved by animal use committees | Merino Sheep | 152 | 152 | 304 |  |
| 172 | Sweden | Uppsala University | Approved by Animal Trials Ethics Committee. Reference no. given. | New Zealand White rabbits | 27 | 243 | 270 |  |
| 173 | USA | Division Neonatal and Respiratory Diseases | No | Monkeys (Macaca nemestrina) | 24 | 24 | 48 |  |
| 174 | USA | Johns Hopkins University; Infectious Disease Branch, NINCDAS | No | Rhesus monkeys | 16 | 16 | 32 |  |
| 175 | Chile; USA | Chile University; University of Texas Southwestern Medical Center | No | Suffolk Down sheep | 25 | 25 | 50 |  |
| 176 | USA | Division of Anesthesiology & Dept Pediatrics; Dept of Pathology | No | Rabbits | 58 | 522 | 580 |  |
| 177 | Australia; USA; Hungary | University of Western Australia; Cincinnati Children’s Hospital; University of Szeged | Approved by animal ethics committee | Sheep | 37 | 37 | 74 |  |
| 178 | USA | University of Wisconsin | Approved by animal use committee | New Zealand White Rabbits | 47 | 423 | 470 |  |
| 179 | USA | Harbor-UCLA Medical Center | No | New Zealand White Rabbits | 46 | 424 *(of which 100 reported in analyses)* | 470 |  |
| 180 | USA | Yale University School of Medicine | No | Sprague Dawley rats | 277 | 3296 | 3573 |  |
| 181 | USA | Harbor-UCLA Medical Center; UCLA school of Medicine | Approved by animal care committee | New Zealand White Rabbits | 17 | 121 | 138 |  |
| 182 | USA | Harbor-university of California; Los Angeles Medical Center | No | New Zealand White Rabbits | 38 | 366 *(of which 192 included in analyses)* | 404 |  |
| 183 | USA; Canada | University Pennsylvania School of Medicine; Children’s Hospital Medical  Center, Cincinnati; University of Western Ontario | Approved by animal care and use committees | Sheep | 112 | 131 | 243 |  |
| 184 | USA | University of Wisconsin, Wisconsin Perinatal Center | No | New Zealand rabbits | 12 | 87 | 99 |  |
| 185 | USA | University of Iowa | No | Rabbits | 20 | 196 | 216 |  |
| 186 | Australia; USA | University of Western Australia; Children’s Hospital Medical Center, Ohio | Protocols were approved by the Animal Ethics Committees at the Children’s Hospital Medical Center and the Western Australian Dept of Agriculture | Sheep | 107 | 107 | 214 |  |
| 187 | Germany | Clinic for Bovine Obstetrics and Gynaecology, College of Veterinary Medicine | No | German dairy cows | 45 | 45 | 90 |  |
| 188 | Australia; USA | University of Western  Australia; Cincinnati  Children’s Hospital | All experimental procedures were approved by the relevant animal experimentation ethics committees. | Sheep | 77 | 77 | 154 |  |
| 189 | USA | University of Vermont College of Medicine | No | Rats | 24 | 216 | 240 |  |
| 190 | USA | University of Miami School of Medicine, Miami | No | Sprague-  Dawley albino female rats | 26 | 233 | 259 |  |
| 191 | USA | Harvard Medical School | No | Sprague-  Dawley rats | 304 | 2736 | 3040 |  |
| 192 | Japan | Sapporo Medical College, Japan | No | Rats  Rabbits  *No. rabbits not reported. Unknown no. animals used in 2 preparatory studies* | 14 | 112 | 126 rats | *An unknown number of foetuses discarded* |
| 193 | Austria | University of Vienna | No | Wistar rats | 60 | 541 | 601 |  |
| 194 | Japan | Kobe University School of Medicine | The study was approved by the Animal Care Committee at Kobe University School of Medicine | Rats | 16 | 135 | 151 |  |
| 195 | USA | Harbor-UCLA Medical Center, UCLA School of Medicine | No | Sheep | 23 | 23 | 46 |  |
| New Zealand White rabbits | 15 | 104 | 119 |  |
| 196 | USA | Albert Einstein College of Medicine, New York City; Yale University School of Medicine, New Haven. | No | New Zealand white rabbits | 26 | 86 | 112 | *About 96* |
| 197 | Canada | McGill University, Montreal | No | New Zealand white rabbits | 21 | 119 | 140 |  |
| 198 | USA | Baylor College of Medicine, Houston | No | New Zealand white rabbits | 25 | 200 | 225 |  |
| 199 | USA | University of California, Harbor General Hospital | No | Sheep | 21 | 32 | 53 |  |
| 200 | USA | John Hopkins University Medical Institutions; University of Chicago; Duke University School of Medicine | No | Dorset sheep | 34 | 43 | 77 |  |
| 201 | Finland | University of Helsinki | No | New Zealand albino rabbits | 83 | 260 | 343 |  |
| 202 | USA | Children’s  Hospital of Los Angeles | No | Western mixed-breed sheep | 27 | 44 | 71 |  |
| 203 | USA | Harbor- UCLA Medical Center, Torrance | No | Sheep  Rabbits  *No. rabbit does/ foetuses unreported* | 23 | 46 | 69 |  |
| 204 | USA; Australia | Harbor- UCLA Medical Center, Torrance; King Edward Memorial Hospital, Subiaco; W Australia Research Institute for Child Health, Perth; W Australia Dept of Agriculture, South Perth | No | Sheep | 85 | 85 | 170 |  |
| 205 | USA | University of California, Los Angeles School of Medicine, Harbor-University of California, Los Angeles Medical Center | No | Mixed breed Western sheep | 12 | 24 | 36 |  |
| 206 | USA | Harbor- UCLA Medical Center, University of California, Los Angeles,  School of Medicine | All animal protocols were reviewed and approved by the Harbor-University of California at Los  Angeles Animal Use Committee according to American Association  for the Accreditation of Laboratory Animal Care guidelines | Sheep | 19 | 19 | 38 |  |
| Rabbits | 4 | 36 | 40 |  |
| 207 | USA | Harbor-University of California; Los Angeles Medical Center | All animal protocols were reviewed and approved by the Harbor-University of California, Los Angeles, Animal Use Committee according to the guidelines  of the American Association for Accreditation of  Laboratory Animal Care | Sheep | 23 | 23 | 46 |  |
| 208 | USA | University of California; Los Angeles School of Medicine | No | Sheep  Rabbits  *No. rabbit does/ foetuses unreported* | 39 | 39 | 78 |  |
| 209 | USA; Australia | Harbor-University of California; Los Angeles, Medical Center; Institute for Child Health Research; King Edward Memorial Hospital | Protocols for these experiments were reviewed and approved by the Animal Use Committee, Harbor-University of California, Los Angeles, Medical Center and the Western Australian Department of Agriculture in accordance with Public Health Service and American Association for Accreditation of Laboratory Animal Care guidelines | Sheep | 30 | 30 | 60 |  |
| 210 | USA | Harbor-UCLA Medical Center; University of California; Los Angeles, School of Medicine | No | Sheep | 26 | 26 | 52 |  |
| 211 | USA | University of California, Los Angeles School of Medicine, Harbor-UCLA Medical Center; University of Texas; Southwest Foundation for Biomedical Research, San Antonio, Texas | All animal husbandry, animal handling, and procedures were reviewed and approved to conform with the American Association for Accreditation of Laboratory Animal Care guidelines as detailed in the Guide for the Care and Use of Laboratory Animals (National Research Council) | Baboons | 10 | 10 | 20 |  |
| 212 | Australia | Monash University | All experimental procedures on animals were approved by the Monash University Animal Ethics Committee | Sheep (Merino x Border-  Leicester) | 22 | 20 | 42 | *Assume 2* |
| **56 studies** | **USA 47; Australia 7; Japan 3; Canada 2; Sweden 1; Chile 1; Hungary 1; ; Italy 1; Netherlands 1; Germany 1; Austria 1; Finland 1 (more than one country can collaborate on a study)** | **Universities 32; Hospitals 4; hospital and university collaboration 17; university and primate research centre 1; hospital, university and pharmaceutical company 1; veterinary college 1** | **Nothing reported 38**  **Statement reported 18**  **(approved by committees 15; according to guidelines 3)** | **Rabbits 25 studies; sheep 22 studies; rats 8 studies; monkeys 4 studies; baboons 2 studies; cows 1 study** | **2665\*** | **13,335\*\*** | **16,000**  **Average no. animals (both mothers and neonates) used per study 286** | **962 at least and likely to be much larger figure** |

\*Sometimes the number of mothers had to be estimated in cases where only the numbers of neonates were reported

\*\* The number of foetuses often had to be estimated, especially for smaller animals, due to poor reporting

**Table B: Antenatal corticosteroids: animal models, anaesthesia, how and when animals killed, what animals experienced**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Animal model** | **Anaesthesia for experimental procedures** (excluding anaesthesia prior to death) | **Fate of mother** | **How foetuses killed** | **When foetus killed (endpoint)** | **What animals experienced** |
| 157 | Model to investigate effect of maternal dexamethasone on neonatal rat | For those foetuses delivered by caesarean section the mother had pentobarbital anaesthesia | Not reported | Not reported | Those delivered by CS killed immediately after delivery. Those delivered vaginally were killed 1 d after birth. | Mothers had drugs 2 days prior to delivery, then underwent delivery naturally or by CS, then had their babies removed from them.  Foetal awareness? Killed as soon as born or one day after. |
| 158 | Model to investigate effect of maternal betamethasone on neonatal lamb | Ewes were sedated for delivery by CS  Foetuses were delivered after sedation with ketamine and placement of an endotracheal tube. | Not reported | Lambs were killed with pentobarbital sodium | Lambs were killed after 40 minutes of mechanical ventilation | A: Mothers had ultrasound, treatment with Depo-provera, then 3 days later IM injections at a range of doses, had their lambs delivered by CS, then had their babies removed from them.  B: A couple of days prior to delivery mothers had IM injections either once or twice, or an intra-amniotic injection. Then a couple of days later had their lambs delivered by CS, then had their babies removed from them.  Foetal awareness of 40 mins of mechanical ventilation? Not clear if they had ketamine before or after this. Foetuses sedated at delivery. |
| 159 | Model to investigate effect of maternal betamethasone on neonatal rabbit | CS delivery under ketamine anaesthesia. | Following completion of the procedure, the doe was killed. We are not told how. | Each foetus had a knot secured around its neck prior to the first breath and its brain, liver, lungs and placenta were removed. Were they strangled to death, or did they die having organs removed? | Foetuses killed upon delivery | Mothers had either CS, or two injections then CS. Then killed.  Foetuses killed upon delivery. |
| 160 | Model to investigate effect of maternal betamethasone on preterm monkey | Not reported (referred to another study) | Not reported | Asphyxiation: the foetal trachea was clamped to prevent spontaneous fetal lung inflation. Death occurred shortly thereafter. | Upon delivery | Mothers had IM injections daily for 3 days, then CS delivery, then had their babies removed from them.  Foetuses killed upon delivery. |
| 161 | Model to investigate effect of maternal betamethasone on preterm baboon | For CS delivery, the pregnant baboons were sedated with IM ketamine  and anesthetized with 1.5% halothane  No foetal / neonatal anaesthesia reported | Not reported | With pentobarbital. | 6 days after delivery | Mothers had 2 ultrasounds; 2 x IM injections prior to delivery, then CS delivery with intubation, then had their babies removed from them.  Neonates intubated, had tracheal instillation of surfactant, IV fluids, 24 h IV glucose infusion, blood taken 4 times, tracheal aspirates taken 12 times, IV bolus radioactive palmitate. No anaesthetic. |
| 162 | Model to investigate effect of maternal T3 / betamethasone on preterm rabbits | None used - mothers killed before delivery  No foetal / neonatal anaesthesia reported | All does were killed by IV administration pentobarbitone on day 27 of pregnancy | Some foetuses presumably died as a result of pressure volume experiment.  Some neonates were left to die ‘naturally’  Some were delivered and decapitated immediately. | Some immediately  Some watched to see how long they could breathe for before dying  We don’t know how long the neonates subjected to the PV experiment lasted for | Mothers had IM injections twice; arterial blood taken, then killed.  Foetuses died of breathing difficulties and others died as a result of experiments. |
| 163 | Model to investigate effect of maternal T3 / betamethasone on preterm rabbits | Does were anaesthetised for CS delivery with intravenous pentobarbital | Not reported | Foetuses were given a lethal intraperitoneal injection of pentobarbital. | Upon delivery | Mothers had IM injections twice, then had CS to deliver babies, which were immediately taken from them.  Foetuses killed at delivery |
| 164 | Model to investigate effect of maternal dexamethasone on preterm monkeys | For CS mothers were given ketamine and atropine IM. A mixture of nitrous oxide/ oxygen was given by inhalation to maintain anaesthesia. | Not reported | A lethal dose of pentobarbital was injected into the fetus to prevent breathing and *a rubber glove* was also placed over the fetal head just prior to delivery. | Just prior to delivery | Mothers had IM injections either as single bolus injection or 4 separate injections. They had blood samples taken 3 times. They had CS to deliver babies and then their babies were taken from them.  Foetuses had blood sample taken from umbilical cord whilst in utero and then killed with pentobarbital and suffocation at delivery. |
| 165 | Preterm rabbit model of respiratory distress syndrome | For 'surgical delivery' does were anesthetized with IV ketamine and pentobarbital  No foetal / neonatal anaesthesia reported | Not reported | We are not told how foetuses were killed | Some were killed at birth, others were killed 1 hour after being mechanically ventilated. | Mothers injected twice, then had CS, then had their babies taken away.  Foetuses:  Some killed at birth  Some had endotracheal tubes placed via a tracheotomy, then injection, then mechanical ventilation for 1hr during which they were paralysed and during which some had pneumothorax. No anaesthetic. |
| 166 | Preterm rabbit model of respiratory distress syndrome | Mothers were given pentobarbital  anaesthesia (250 mg iv) for CS  No foetal / neonatal anaesthesia reported | Not reported | We are not told how foetuses were killed. | Some foetuses were killed after 1 hour of mechanical ventilation  Some foetuses were killed at birth | Mothers injected twice, then had CS, then had their babies taken away.  Some foetuses killed at birth.  Some foetuses paralysed but not anaesthetised, had metal cannula inserted through larynx, given treatment or vehicle by injection into trachea, had chest and abdomen pressed, then ventilated, then transferred to another chamber and ventilated at higher pressure, with measurements that involved clamping the trachea 3 times. Then killed. Some suffered pneumothorax. Some of their tracheas too small for cannulas |
| 167 | Preterm rabbit model of respiratory distress syndrome | The does received intravenous pentobarbital for  light anaesthesia and oxygen by face mask. The abdominal wall  was anesthetized with 1% lidocaine.  No foetal / neonatal anaesthesia reported | Not reported | Each rabbit was disconnected from the ventilator and killed with an intracerebral injection of lidocaine that stopped the heart immediately | 30 mins after initiation of ventilation | Mothers had either: IM drugs or vehicle twice, then CS delivery, or IM and IV drugs once, then CS delivery and babies taken away.  Preterm rabbits had no anaesthesia but had a neck incision, a tube tied into the trachea and drugs delivered through trachea. Then ventilated manually for five breaths, then transferred to ventilator for 30 mins (during which six rabbits had pneuomothoraces). Had drugs delivered through jugular vein. |
| 168 | Preterm rabbit model of respiratory distress syndrome | For CS delivery does anaesthetised with IV pentobarbital and oxygen by face mask.  Lidocaine with epinephrine used as supplemental anaesthesia  for abdominal wall.  neonates anaesthetised with IP ketamine and acepromazine | Not reported | Each fetal rabbit was killed with an intrathecal injection of lidocaine | After 30 min of ventilation | Mothers given IM drugs or vehicle twice, then either CS delivery or natural delivery and babies taken away.  All newborns were allowed to breathe for 1-3 hours prior to experiments.  Rabbits anaesthetised, had a neck incision and a tube tied into the trachea. Drugs delivered through endotracheal tube. Rabbits then ventilated manually, then transferred to ventilator for 30 mins. Had drugs delivered through jugular vein. |
| 169 | Preterm rabbit model of respiratory distress syndrome | For CS delivery mothers lightly anaesthetised with IV sodium pentobarbital and oxygen by face mask. Supplemental local lidocaine anaesthesia for abdominal wall incision.  No anaesthesia for neonates | Not reported | Each rabbit was killed with an intrathecal injection of lidocaine and disconnected from the ventilator. | After 30 mins of ventilation. | Mothers given IV drugs or vehicle 2 – 4 times, then CS delivery, then babies taken away.  Foetuses not given anaesthesia, incision made in neck to secure tube in trachea, given agent through tracheal tube, then ventilated manually, then in ventilator. Injection via external jugular vein. |
| 170 | Preterm sheep model of respiratory distress syndrome | For CS delivery ewes sedated with IM ketamine  and had spinal anaesthesia (lidocaine).  Foetuses were sedated with IM ketamine and their necks were anesthetized subcutaneously with lidocaine.  Later they were given pentobarbital by slow arterial infusion. | Not reported | Each lamb was given pentobarbital (30 mg/kg), the tracheal tube was clamped for 3 min, followed by exsanguination. | 40 mins after birth | Mothers had IM drugs or saline five times. They were allowed to freely feed in paddocks between injections and were not handled other than for the injections. They then had CS delivery and babies taken away.  Foetuses sedated and anaesthetised, had endotracheal tube placed, then delivered, then artificially ventilated. Had arterial catheter placed through which given pentobarbital. Had blood samples taken at least twice. |
| 171 | Preterm sheep model of respiratory distress syndrome | Ewes sedated with IM ketamine and zylazine and had spinal anaesthesia (lidocaine).  Foetuses sedated with IM ketamine and zylazine. Their anterior foetal necks were anesthetized with lidocaine, subcutaneously. | Not reported | Each lamb given pentobarbital (30 mg/kg). | 40 minutes after birth | Mothers had 1 injection (Depo Provera) then 1 or 3 doses of IM drugs. Then had CS delivery and babies taken away.  Foetuses anaesthetised, had tracheotomy, endotracheal tube place. At least two blood samples taken. Ventilated for 40 mins. Had arterial catheter placed and slow arterial infusion of pentobarbital. |
| 172 | Model to investigate effect of maternal betamethasone on preterm rabbits | For CS delivery mothers given IV  ketamine followed by spinal or epidural  anaesthesia (bupivacaine) | Nothing reported | Pups were killed by a s.c. injection of thiopental  sodium in the nuchal region. A string was subsequently tied around the neck to prevent fluid escape from the airways. | Immediately after birth | Mothers had one or two s.c. injections, followed by CS delivery under anaesthetic, then babies taken away.  Foetuses killed upon delivery by thiopental followed by strangulation |
| 173 | Monkey model of respiratory distress syndrome | Each mother received an IM injection of succinylcholine chloride, ketamine hydrochloride and atropine sulfate and was ventilated with a mixture of oxygen (40%) and nitrous oxide (60%). Analgesia  supplemented with local infiltration of the incision site with xylocaine. Anaesthesia with halothane was begun after delivery of the foetus.  Foetuses had tracheostomy performed under local anaesthesia | Nothing reported | Foetuses were killed by intravenous injection of sodium pentobarbital | 3 hours after birth | Mothers had IM injections, then CS delivery under anaesthetic, with analgesia, then had their babies taken away.  Preterm monkeys were resuscitated upon delivery, then had rectal probe inserted, and arterial and venous catheters inserted, then arterial infusion of Dextrose. They had tracheostomy performed under local anaesthetic. They were paralysed then mechanically ventilated, had agent infused through catheter, had chest x-ray, blood samples taken, then killed with IV injection. |
| 174 | Monkey model of respiratory distress syndrome | Nothing reported | Nothing reported | The foetal trachea was clamped immediately on delivery before the foetus could inspire any air. The trachea was dissected free and slit open. | Foetal death occurred shortly after the trachea was clamped, upon delivery. | Mothers had IM injections daily for 3 days or 13 days prior to CS, had CS delivery, then their babies removed.  Foetuses killed upon delivery. |
| 175 | Model to investigate effect of maternal betamethasone and / or TRH on preterm lambs | Catheters placed in ewes under light ketamine anaesthesia.  Ewes had CS delivery under thiopental sodium anaesthesia. | Nothing reported | All foetuses killed by overdose of IV thiopental sodium | Upon delivery, before initiation of breathing. | All mothers had one IM injection, antibiotics, and catheters placed under anaesthesia. Mothers had IV and / or IM agents over 2 days prior to CS. All mothers had blood samples taken daily, then CS delivery, then their babies taken away.  Foetuses killed upon delivery by IV injection. |
| 176 | Rabbit model of RDS to compare maternal versus foetal delivered drugs | Mothers having laparotomies  were anaesthetized with halothane.  The foetuses were delivered by CS under halothane anaesthesia.  No foetal / neonatal anaesthesia reported | Nothing reported | Some rabbits were killed before their first breath by severing the cervical cord and their lungs were removed immediately.  Others were left to struggle for breath, presumably until they died. | Some killed upon delivery. Others left to die, with some taking up to two hours to die. | Mothers had either IM injection 3 times, then CS delivery, then babies taken away, OR laparotomy under anaesthesia, then CS delivery 2/3 days later, then babies taken away.  Foetuses either killed immediately or left to gasp for breath until they died, with some taking up to 2 hours to die. |
| 177 | Sheep model of RDS | For delivery ewes were sedated with IM ketamine and xylazine prior to spinal anaesthesia with lidocaine.  The foetus was sedated with IM ketamine and xylazine, and local anaesthetic on anterior neck (lidocaine s/c). | Not reported | Lambs were killed with pentobarbitone, the endotracheal tube clamped, and the lungs excised. | At 40 mins of age, I think. | Mothers had progesterone (injection?), then weekly IM injections (some had several weeks’ worth, some fewer), then CS delivery, then had babies taken away.  Foetuses sedated/ anaesthetised for tracheotomy, then delivered and mechanically ventilated (for 40 mins I think), had arterial line placed and pentobarbital given to suppress breathing if necessary, then killed. |
| 178 | Rabbit model of RDS | Nothing reported  No foetal / neonatal anaesthesia reported | All does were killed on day 27 by pentobarbital sodium injection into ear vein. | The authors do not say if they killed the foetuses or if they just allowed them to die. | Not reported | Mothers either handled, given saline, or 1 or more courses of betamethasone, then killed by pentobarbital injection.  Foetuses delivered from dead mothers, fate unknown. |
| 179 | Rabbit model of RDS | For CS delivery does were medicated with IV diazepam and given spinal anaesthesia (lidocaine hydrochloride-bupivacaine hydrochloride)  On delivery, preterm rabbits used for foetal wash, ventilation, or pressure-volume  measurements received ketamine and acepromazine by IP injection. | Not reported | Foetuses were killed with an intrathecal  injection of lidocaine | Some were killed immediately after tracheostomy, some were killed after 30 minutes of ventilation, some were killed after 10 breaths on ventilator and plugging of tracheal tube, | Mothers were weighed, had IM injections daily for 2 days before CS, then CS under sedation and anaesthesia, then had babies taken.  All foetuses had IP anaesthesia, weighed, then tracheostomy. Then some killed immediately; some given IV agent and ventilated (during which 11 had pneumothoraces), then killed; some ventilated briefly and had tracheal tube plugged for 5 mins, then killed. |
| 180 | Rat model to investigate effects of maternal dexamethasone and /or T3 on foetuses and new-borns | Nothing reported  No foetal / neonatal anaesthesia reported | Mothers who delivered by CS were killed by decapitation after concussion, prior to CS delivery. Not clear how they were concussed. Not clear what happened to mothers who delivered spontaneously | Foetuses and new-borns were killed by decapitation. | Presumably foetuses and new-borns killed immediately upon delivery. | Mothers had one or two injections for two days, then some killed. Others delivered their babies spontaneously and had babies with them for one day before they were taken away.  Foetuses and new-borns either killed immediately upon delivery or kept with mother for one day and then killed. |
| 181 | Rabbit model of RDS | Mothers anesthetized with pentobarbital followed by spinal anaesthesia with lidocaine and bupivacaine.  Baby rabbits given IP acepromazine and ketamine upon delivery. | Not reported | The endotracheal tube was obstructed, and the rabbit was killed with intrathecal lidocaine. | After 30 minutes of ventilation. | Mothers had IM injections on one or two days before having CS delivery under light anaesthesia. Then their babies were taken away.  Preterm rabbits were delivered, anaesthetised, had tracheal tube placed and some were given sheep surfactant. Rabbits were given five breaths then ventilated for 30 mins, given IV injection, then killed by obstruction of airway and intrathecal lidocaine. |
| 183 | Sheep model of RDS | Not reported.  No foetal / neonatal anaesthesia reported | Not reported | The lambs were killed with an overdose of pentobarbital sodium followed by  exsanguination | Presumably killed after ventilation, so either at 40 minutes for some, or 4 hours for others | Mothers had ultrasound, then depo-provera injection. Then some had 1-4 doses of drugs either 15 hours, 48 hours, or weekly 3 weeks before CS delivery. Then either CS delivery and babies taken away. Others had procedures whereby their foetuses had ultrasound-guided intra-amniotic or foetal IM injections at the same times, then CS delivery, then babies taken away.  Some foetuses had ultrasound-guided intra-amniotic or foetal IM injections, then delivered, others had intratracheal beractant, others just delivered. All foetuses ventilated, some for 40 mins, some for 4 hours before being killed. |
| 182 | Rabbit model of RDS | For CS mothers lightly anaesthetised with IV diazepam, given supplemental oxygen via a face mask and also spinal anaesthesia.  New-born rabbits given ketamine and acepromazine anaesthesia by IP injection. | Not reported | New-born rabbits were killed with intrathecal injections of lidocaine and the chest opened. | After 30 minutes of ventilation | Mothers had 1-4 injections delivered both IV and IM, then CS delivery, then babies taken away.  Foetuses had IP anaesthesia, then tracheal tube placed, during which some had ‘upper airway leaks’ during placement. Some foetuses had agent injected into trachea. All foetuses given 5 breaths then ventilated for 30 mins, during which some had pneumothoraces. All had agent injected via jugular vein. All killed with injection lidocaine. |
| 184 | Rabbit model to investigate effect of maternal hydrocortisone phosphate on preterm babies | Mothers anesthetized with IV pentobarbitol prior to death by thoracotomy.  No foetal / neonatal anaesthesia reported | At day 27 mothers killed by thoracotomy. | Foetuses killed by clamping of the trachea and exsanguination by cutting through abdomen to remove lungs and liver. | Upon delivery | Mothers had IM injections every 8 hours for three days then killed by thoracotomy under anaesthesia.  Foetuses delivered, had tracheas clamped, stomachs cut open and organs removed. No anaesthesia. |
| 185 | Rabbit model to investigate effect of maternal betamethasone on new-borns | Halothane in oxygen for delivery by CS.  No foetal / neonatal anaesthesia reported | Not reported | Some pups left in amniotic sacs to suffocate. Think for others it was an overdose of anaesthesia, but this is unclear. | Some on delivery, others at 6 hours, one day or two days post delivery | Mothers had injections for 2 days, then CS delivery, then babies taken.  Some new-borns suffocated in amniotic sacs, all others given injection of fluids some of which also had fluids by nasogastric tube, then killed at various time points post delivery |
| 186 | Sheep model of RDS | Nothing reported  No foetal / neonatal anaesthesia reported | Not reported | We are not told how the foetuses were killed | We are not told when foetuses were killed but presumably after 40 minutes of ventilation. | Mothers were weighed and had IM injection progesterone, then either 3 IM injections every 7 days, or procedure whereby their foetuses had 3 IM injections using ultrasound, then CS delivery, then their babies taken away.  Foetuses were either delivered by CS, or had 3 ultrasound guided IM injections while in the womb, then delivered by CS, then ventilated for 40 mins, then presumably killed. |
| 187 | Cow model of RDS | Local anaesthesia for laparotomies (lidocaine).  Local anaesthesia for CS delivery (not told what anaesthetic).  No foetal / neonatal anaesthesia reported | Not reported | Not reported | Not reported, but calves observed up to 24 hours after preterm delivery | Mothers had laparotomies under local anaesthesia, then IM injection, then CS delivery under local anaesthesia, 3 blood samples taken, then babies taken away.  Calves ‘exteriorised’ whilst in utero for collection of amniotic fluid, then delivered 42 hours later, blood samples taken four times, then observed for up to 24 hours. 8 calves died during experimentation and 14 calves assessed to have RDS. We don’t know if/ how/ when killed. |
| 188 | Sheep model of RDS | For CS delivery sedation with ketamine and xylazine. Also spinal anaesthesia (lidocaine).  Prior to killing, the lambs were were anesthetized deeply with pentobarbital  No foetal / neonatal anaesthesia reported | Not reported | Lambs deeply anaesthetized deeply, tracheal tube clamped for 3 minutes, then ‘exsanguinated’ | At 40 minutes of age | Mothers had IM progesterone, then either injections into rump or restrained for ultrasound guided procedure to aspirate fluid, then intra-amniotic injections. Returned to field then CS delivery, then babies taken away.  Foetuses either delivered or had intra-amniotic injection, then delivered. During delivery foetuses had endotracheal tube placed (no anaesthesia), fluid aspirated, then delivered. Ventilated for 40 mins, during which some lambs had pulmonary interstitial emphysema and / or pneumothoraces. Catheter placed into aorta, blood taken every 10 mins, then killed. |
| 189 | Rat model to investigate effect of maternal corticosteroids on preterm lungs of babies | Presumably no anaesthesia for delivery as mothers killed prior to CS.  No foetal / neonatal anaesthesia reported | Mothers killed on day 21, presumably prior to delivery. We are not told how they were killed. | We are not told how the foetuses were killed, either those used or not used in the experiments. | Not reported, presumably upon delivery | Mothers had IP injections, then killed. |
| 190 | Rat model to investigate effect of maternal dexamethasone on new-born rats and foetuses. | Main experiment: mothers had pentobarbital anaesthesia for hysterotomy  Survival studies: mothers had hysterotomy  under ketamine and xylazine anaesthesia  No foetal / neonatal anaesthesia reported | Not reported | Not told clearly how foetuses were killed. Presumably most died of breathing difficulties. There is a reference to exsanguination so perhaps some were killed in this way. | Not reported. | Mothers had IP drugs, then hysterotomy surgery under anaesthesia, then babies taken away.  Foetuses delivered early, transferred to warmed cage. Fate unknown |
| 191 | Rat model to investigate effect of maternal dexamethasone on foetuses. | Not reported  No foetal / neonatal anaesthesia reported | Mothers were decapitated prior to preterm delivery of their babies. | Foetuses appear to have been left to die in the uteri which were removed and placed in iced saline. | Upon delivery | Mothers weighed an unspecified number of times, injected IP with agent, then decapitated 24 hours later.  Foetuses were delivered, placed in ice, weighed and lungs removed. No anaesthesia reported. |
| 192 | Rat model to investigate effects of dexamethasone on lungs of mothers, foetuses and new-borns | Anaesthesia not even mentioned, not for any of the procedures  No foetal / neonatal anaesthesia reported | Not reported | Not reported | Not reported. Presumably foetuses killed at delivery, new-borns at some point up to five days and mothers just before or after delivery. | Mothers injected IP with agents then killed. Not clear whether foetuses delivered before or after death. Foetuses delivered preterm. New-borns studied for either 1, 3 or 5 days. |
| 193 | Rat model to investigate effect of maternal betamethasone on foetuses. | Not reported | We are not told what happened to the mothers | All foetuses were killed by clamping of the trachea before spontaneous breath could occur. The foetuses then had thoracotomies & lungs removed. | Foetuses killed immediately after delivery. | Mothers either had IP agents injected, then CS delivery, then babies taken away, OR just CS delivery and babies removed. Foetuses killed upon delivery by clamping trachea and thoracotomy |
| 194 | Rat model to investigate effect of maternal agent on foetal lungs. | Not reported | Pregnant rats were killed by a lethal inhalation of diethyl ether | Foetal rats were killed by decapitation. | Mothers killed on day 20 gestation prior to delivery. Foetuses killed at delivery | Mothers had IP injections for three days, then killed by decapitation. Foetuses killed upon delivery. |
| 195 | Sheep model of RDS  Rabbit model of RDS | Ewes were anaesthetized for CS with IM ketamine and atropine. They also had spinal-epidural anaesthesia (lidocaine and marcaine).  Lamb foetuses had IM ketamine and acepromazine. The skin and subcutaneous  tissues over the anterior neck were infiltrated with lidocaine.  Rabbits mothers were anaesthetized with IV pentobarbital  followed by spinal anaesthesia (lidocaine  and bupivacaine).  Rabbit foetuses were anaesthetized  IP ketamine  and acepromazine | Fate of mother sheep and rabbits not reported | Each lamb was anesthetized deeply with IV pentobarbital and the endotracheal tube was clamped for 3 minutes. Lambs were then exsanguinated via abdominal aorta.  The endotracheal tubes of the rabbit foetuses were plugged for 5 minutes. | Preterm lambs killed after 3 hours of ventilation  Rabbit foetuses killed after 15 minutes of ventilation | Pregnant ewes had procedure to deliver ultrasound guided IM injection of agent to foetuses, then CS delivery under anaesthesia, then babies taken away.  Lamb foetuses had IM injection, then two days later delivered preterm, anaesthetised, had endotracheal tube placed by tracheostomy, had lung fluid withdrawn, endo-tracheal tube clamped, were weighed, had intra- tracheal instillation, were ventilated for 3 hours, had catheter placed in aorta, given dextrose infusion, given IM agents to prevent breathing, given injection of albumin then killed.  Pregnant rabbits given surfactant, anaesthetised, had CS delivery, then babies taken away.  Rabbit foetuses weighed, anaesthetised, had tracheal tube placed, some had surfactant, all ventilated for 15 minutes then killed. |
| 196 | Rabbit model to investigate effect of foetal cortisol on foetuses | Mothers anaesthetized with halothane or ether, for laparotomies.  We’re not told if mothers were anaesthetised for hysterotomies.  No foetal / neonatal anaesthesia reported | Not reported | Most foetuses had their necks tied immediately upon delivery.  Others had the cervical cord severed and thoracotomies. Remainder presumably left to die of breathing difficulties? Unknown. | Some upon delivery  Some between 10 minutes and 2 hours of age | Mothers had laparotomies under anaesthesia, then hysterotomies to deliver babies (anaesthesia?), then babies taken away.  Foetuses had injection into abdomens in utero, then preterm delivery, then either strangled upon delivery, observed for up to 2 hours (unknown if these left to die), or killed. |
| 197 | Rabbit model to investigate effect of foetal hydrocortisone hemissuccinate and barium sulphate on rabbit foetuses | Pregnant rabbits were  operated on under halothane  anaesthesia.  For delivery of foetuses the doe was stretched on its back, its eyes were covered, and traction was applied to its neck and head to quieten it sufficiently for incision to be reopened and foetuses removed.  No foetal / neonatal anaesthesia reported | Does were killed after foetuses delivered. We are not told how. | Foetuses were left to die of breathing difficulties. | The time it took foetuses to die depended upon which treatment group they were in. Time to death could take up to 6 hours. | Mothers had operation under anaesthesia to inject foetuses with agent, then two days later wound reopened without anaesthesia and foetuses delivered, then mothers killed.  Some foetuses injected in utero, then delivered preterm, placed in observation box and left to die. |
| 198 | Rabbit model to investigate effect of foetal aminophylline and dexamethasone on foetuses | Mothers were anaesthetized by inhalation of methoxyflurane in a mixture of air and oxygen for operation to expose uterus.  CS delivery was also under anaesthesia. | We don't know what happened to the mothers. | Foetuses were killed by IP injection of pentobarbital | Foetuses were killed immediately upon delivery | Mothers had operation under anaesthesia to allow foetal injections, then recovery of 2.5 hrs, then CS delivery under anaesthesia.  Foetuses had IP injection in utero, then delivered preterm, then killed. |
| 199 | Sheep model of RDS | Non-steroid treated group: ewes had local anaesthesia CS delivery. Foetuses had tracheostomy under local anaesthesia.  Steroid treated group: Ewes had hysterotomy under local anaesthesia. We are not told if they had anaesthesia for CS delivery later on. | Not reported | We are not told how the non-steroid treated animals were killed.  We are not told how the steroid treated foetuses were killed. In this group the control twin was left to die from breathing difficulties.  Some foetuses died from circulatory failure. | Non-steroid treated foetuses killed between 2 and 5 h of age.  We are not told when the steroid treated foetuses were killed. All control animals died within 30 minutes. | Some mothers had CS delivery under local anaesthesia and their babies taken away. Others had hysterotomy under local anaesthesia to allow their foetuses to be catheterised and then must have had external catheters affixed to allow administration of IV drugs every 8-12 hours for 4-14 days, then CS delivery, then their babies taken away.  Some foetuses had tracheostomies at delivery under local anaesthesia, then suction, then ventilation (2-5 hours?), catheters placed in an artery and a vein, one or two injections through catheters, then killed. Others had catheters placed in jugular vein while in utero and drugs delivered for 4-14 days, then delivered preterm, ventilated, catheterised and killed. Other foetuses delivered preterm and left to die. |
| 200 | Sheep model to investigate effect of foetal hyrdrocortisone on foetuses | Ewes whose lambs had uterine procedure had general anaesthesia (halothane in oxygen, IV succinylcholine) which was maintained with halothane and nitrous oxide in oxygen. These ewes also had pancuromium bromide as a 'muscle relaxant'.  Some also had spinal anaesthesia (Tetracaine with epinephrene)  All ewes were anaesthetised for CS delivery (IV pentathol).  No foetal / neonatal anaesthesia reported | We aren't told what happened to the ewes. | New-born lambs had their tracheas clamped and were killed with IV pentathol. | Lambs were killed immediately upon delivery | Some mothers had general anaesthesia with tracheal intubation/ ventilation for operation for procedures to their foetuses, had arterial catheters inserted, then had foetal catheters coming through an incision in their flanks, then CS delivery under anaesthesia, then babies taken away. Other mothers just had CS delivery under anaesthesia then babies taken.  Foetuses had catheterisation in utero and IP injections daily for 3-5 days, then delivered, tracheas clamped and killed. Other foetuses were simply delivered preterm and killed immediately. |
| 201 | Rabbit model to investigate effect of maternal or foetal ritodrine, or foetal betamethasone on foetal RDS | The pregnant does were  operated upon under local anaesthesia (lidocaine without adrenalin)  No foetal / neonatal anaesthesia reported | Not reported | New-born rabbits were killed with an intracerebral injection of phenobarbital | After being allowed to breathe for 5 or 30 minutes. | Mothers had either IM injections or procedure under local anaesthetic to administer drugs to foetuses, then CS delivery under local anaesthetic, then babies taken away.  Foetuses had IM injections in utero and/ or IP injection at delivery, preterm delivery and then left for either 5 or 30 minutes to breathe before being killed by injection. |
| 202 | Sheep model of RDS to investigate effect of various foetally administered agents | 19 ewes had epidural anaesthesia with local anaesthetic (pontocaine) for their operations  No foetal / neonatal anaesthesia reported | Ewes killed with a rapid IV injection of sodium pentobarbital | Foetuses killed with a rapid IV injection of sodium pentobarbital | All animals killed between 130 - 134 days gestation at the end of hormone infusions | Mothers had operation under local and general anaesthesia, after which they had 3 catheters coming out of their flanks and a latex bag left in uterus. Then 7 days during which infusions given to /fluids taken from foetuses, then killed.  Foetuses had operations in utero, with no anaesthetic, to place catheters in artery, vein and trachea, then infusions, tracheal fluid taken daily, blood taken three times, then killed. |
| 203 | Sheep model of RDS to investigate effect of foetal administered agents on foetuses | First operation: ewes had IM atropine and ketamine followed by continuous intravascular infusion with ketamine. Local anaesthesia was lidocaine.  CS delivery: ewes pre-anaesthetised with atropine and ketamine IM, then continuous infusion ketamine and local anaesthesia for tracheostomy.  Foetus: at delivery, after head and neck exposed, foetuses received IM ketamine and acepromazine. They also had local anaesthesia with lidocaine for tracheostomies. | Not reported | Each lamb given IV pentobarbital after which endotracheal  tube clamped to permit resorption atelectasis over 5 minutes. Chest wall then incised and heart removed. | After 1.25 hours of ventilation | Ewes had operation under anaesthesia to perform procedures on foetuses, after which they presumably had 2 exterior catheters for infusions. Then antibiotics, then a week later ewes had tracheostomy under anaesthesia, then CS under anaesthesia, then babies taken.  Foetuses had 2 catheters placed in utero, no anaesthesia, then constant IV infusions and five bolus injections over 1 wk. Then CS delivery, then anaesthesia for placement of endotracheal tube, removal of foetal lung fluid, ET tube clamped, lamb weighed, dried, venous cord blood sampled, then agents and albumin via endotracheal tube, then ventilated, umbilical artery placed, then killed after 85 mins of ventilation. |
| 204 | Sheep model of RDS to investigate effect of foetal administered agents on preterm lambs. | For CS ewes had IM ketamine, then spinal-epidural anaesthesia  with lidocaine.  Foetuses received IM ketamine and local anaesthesia with lidocaine on foetal neck.  After initiation of  ventilation, lambs received pentobarbital sodium by slow arterial infusion to block spontaneous breathing ventilation. | Nothing reported | Lambs killed with an overdose of pentobarbital followed by exsanguination | After 50 minute study period following delivery. | Mothers had ultrasound at 50 days gestation. At 126/7 days they were placed in sitting position to give foetal drugs under ultrasound (no anaesthesia for ewe). 1 or 2 days later mothers given CS delivery, then lambs taken away.  Foetuses had IM or intravascular injections of betamethasone, saline or hydrocortisone. A couple of days later they were delivered preterm, had tracheotomy performed under anaesthesia and endotracheal tube placed. Lambs dried and ventilated for 50 mins, arterial catheter placed, glucose infused, spontaneous breathing prevented, blood taken then killed. |
| 205 | Sheep model of RDS to investigate effect of foetal administered agents on preterm lambs | Ewes were pre-medicated with IM ketamine and atropine, then anaesthetised with isoflurane for hysterotomy (for procedure to foetus).  For CS delivery ewes were anaesthetised.  Ketamine and acepromazine were given IM to the foetus and local anaesthetic (lidocaine) was administered to the foetus' neck. | Not reported | Animals were killed with a pentobarbital sodium overdose, weighed and organs removed | At 2 hours of age | Ewes had hysterotomy under anaesthesia for procedures to foetuses, then catheters stored on ewe’s flank in pouch. Ewes had antibiotics, then infusions given to foetuses via catheters. Then CS delivery, then babies taken away.  Foetuses had catheters placed in utero, antibiotics, then infusion of agents for 60 hours, then preterm delivery, tracheostomy under anaesthesia, ET tube secured, then ventilated for 2 hours, artery catheterised, given surfactant by tracheal instillation, 6 blood samples taken, dextrose infused. |
| 206 | Sheep model to investigate effect of foetal agents on preterm lambs, then rabbit model to investigate effect of treated lamb surfactant on preterm rabbits | Not reported for ewes.  Rabbits anaesthetized with IP ketamine and acepromazine  Each preterm lamb had IM ketamine and acepromazine to prevent spontaneous breathing, but not necessarily for anaesthesia | Neither the fates of the pregnant ewes, nor pregnant rabbits are reported | The lambs were deeply anesthetized  with intravascular pentobarbital, the endotracheal tube was clamped for 3 minutes to permit oxygen reabsorption, and  the animals were exsanguinated.  Rabbits had the endotracheal tube plugged for 5 minutes to allow absorption atelectasis to occur and were then killed with intrathecal lidocaine. | Lambs killed after the 2 hour post-delivery study period  Rabbits killed after 15 minutes of ventilation | Ewes: nothing reported.  Foetuses injected in utero, delivered preterm two days later, had tracheostomy to secure ET tube, no anaesthesia reported, had lung fluid aspirated and ET tube clamped, weighed, ventilated for 2 hours with IM agents injected to prevent spontaneous breathing, catheter placed in aorta, infusion of dextrose, blood samples taken, then killed.  Rabbits delivered, weighed, anaesthetised, tracheas cannulated, some had agents delivered via tracheal tube (some did not), manual, then mechanical ventilation, death. |
| 207 | Sheep model to investigate effect of foetally administered agents on preterm lambs | No information on anaesthesia used for ewes while foetal injection or CS delivery performed  Each preterm lamb had IM ketamine and acepromazine to prevent spontaneous breathing, but not necessarily for anaesthesia | Not reported | Lambs were deeply anaesthetized with intravascular  pentobarbital, the endotracheal tube clamped  for 3 minutes to permit oxygen reabsorption and animals exsanguinated | The post-delivery period of study was 1 hour, presumably they were killed after this. | Ewes had ultrasound and procedure to inject foetuses, then CS delivery, then lambs taken away.  Foetuses had IM injections in utero, then delivered preterm, had tracheostomy and ET tube placed, apparently with no anaesthesia, had blood taken, IM agents to prevent spontaneous breathing, ventilated for an hour, catheter placed in aorta, given albumin through catheter and dextrose through catheter, blood taken, killed. |
| 208 | Sheep model to investigate effect of maternal and/ or foetal agents on preterm lambs, and the effect of preterm lamb surfactant on preterm rabbits | No information on anaesthesia used for ewes while foetal injection performed.  For delivery, each ewe sedated with IM ketamine and anaesthetized using spinal-epidural anaesthesia.  Foetus sedated and anaesthetized (ketamine with acepromazine IM, lidocaine SC at the site of incision).  No information on anaesthesia for rabbits. | Fate of pregnant ewes not reported  Fate of pregnant rabbits not reported | The lambs were deeply anesthetized (pentobarbital sodium given via umbilical catheter), the tracheal tube was clamped during expiration to allow for oxygen reabsorption from the lungs.  Rabbits: the tracheal tube was plugged for 5 minutes and the animals were then killed with an intrathecal injection of lidocaine | After 4 hours of ventilation  After 15 minutes of ventilation | Ewes had agents injected into them, as well as ultrasound guided IM injections of agents into their foetuses, then CS delivery under anaesthesia and procedures done to foetuses at delivery, then their babies taken away.  Lamb foetuses had IM injections in utero, then preterm delivery at which they were sedated, anaesthetised, had tracheostomies and ET tubes placed, lung fluid withdrawn, tracheal tube clamped, given agent for RDS, ventilated for four hours, catheter place in aorta, arterial line placed, blood samples taken, infusion of dextrose, hypoxic challenge, albumin via catheter, killed.  Rabbit foetuses delivered preterm, had tube tied into trachea (no anaesthesia mentioned) and most given surfactant (controls not given agent), lungs inflated, ventilated for 15 minutes, tracheal tube plugged for 5 minutes, killed. |
| 209 | Sheep model to investigate effect of foetal betamethasone on preterm lambs | No information given on anaesthesia for foetal injection  For delivery ewes were sedated with IM ketamine,  and had spinal anaesthesia  (lidocaine)  At delivery the foetus was sedated with IM ketamine and the  anterior foetal neck was anaesthetized with sc lidocaine | Not reported | Lambs were killed with an overdose  of pentobarbital followed by exsanguination | 40 minutes after birth | Ewes had 2 procedures to inject foetuses, then CS delivery and procedures to foetuses under sedation/ anaesthetic, then lambs taken away.  Foetuses had 2 IM injections whilst in womb, then at preterm delivery sedated/ anaesthetised, had tracheotomy and ET tube placed, blood taken, dried, ventilated for 40 minutes, arterial catheter placed, dextrose infused, pentobarbital to prevent breathing, more blood taken, killed. |
| 210 | Sheep model to investigate effect of foetal and maternal betamethasone on preterm lambs | No information given on anaesthesia to ewes for foetal injection.  For CS each ewe was sedated with ketamine and had spinal-epidural anaesthesia (lidocaine-marcaine solution)  The foetus had sedation with ketamine and  acepromazine and local anaesthesia with lidocaine  After delivery, supplemental IM ketamine and  acepromazine were given for sedation and  analgesia. | Not reported | Animals were deeply anesthetized with pentobarbital sodium and the tracheal tube was clamped. The animals were killed by exsanguination, achieved by cutting the abdominal aorta. | After 4 hours of ventilation | Mothers had injections and procedures to inject their foetuses, then CS to deliver lambs and for procedures to lambs at delivery, under anaesthesia, then lambs taken.  Foetuses had IM injections while in utero, then at preterm delivery were sedated/ anaesthetised, had tracheotomy and ET tube placed, tracheal fluid aspirated, ET tube clamped, weighed, given surfactant whilst being rotated, ventilated for 4 hours, 2 catheters placed, blood given, blood taken, dextrose given, radiolabelled microspheres given, some withdrawn, killed. |
| 211 | Baboon model to investigate effect of foetal betamethasone on preterm baboons | The pregnant baboons were sedated with IM  ketamine for each of the prenatal  ultrasounds.  For CS delivery baboons were sedated with ketamine, intubated and anesthetized with halothane.  New-born baboons were maintained sedated with IM  ketamine and IV diazepam if needed. Local anaesthesia with lidocaine and additional ketamine were administered for any invasive procedures.  Prior to killing, each baboon  Had pentobarbital to achieve deep anaesthesia | After delivery of the foetus and repair of the maternal incisions, recovery of the female baboons was monitored daily for 2 weeks, with all animals released to outside gang cages after 4 weeks. | Prior to killing baboons had pentobarbital sodium to achieve deep anaesthesia and were ventilated for 2 minutes with 100% O2. The endotracheal tube was disconnected from the ventilator to allow passive deflation of the lungs and was clamped. Cardiac activity continued for 2 minutes to permit absorption atelectasis and was followed by pentobarbital and exsanguination. | After 24 hours | Mothers had amniocentesis and ultrasound, then ultrasound to inject foetuses, both under sedation, then a day later CS delivery and procedures to foetuses under sedation and anaesthesia, then babies taken away. Monitored daily for 2 weeks before release to outside cages after 4 weeks.  Foetuses had IM injection while in utero, then at preterm delivery and onwards had sedation and anaesthesia. Foetuses intubated using ET tubes, given surfactant by tracheal instillation, ventilated for 24 hours, had arterial and venous catheters placed, given IV inulin, parenteral fluids, antibiotics, adult baboon blood. Blood samples and plasma taken. Monitored continually, injected with labelled albumin, killed. |
| 212 | Sheep model to investigate effect of foetal cortisol and foetal cortisol and lung liquid drain, on foetuses | We are not given any information on anaesthesia for the ewe during surgery or any procedures  No foetal / neonatal anaesthesia reported | The ewe was killed with an overdose of pentobarbitone sodium administered IV to the ewe | The foetus was killed with an overdose of pentobarbitone sodium administered IV to the ewe. (Foetuses not delivered – all procedures done in utero) | At 131 days gestation, 22 days after commencement of the study period | Mothers had surgery for implantation of vascular catheters and for implantation of catheters in their foetuses. Mothers then had procedures done to their foetuses via these catheters for 22 days, then killed.  Foetuses had vascular and bi-directional foetal tracheal catheters implanted in utero. All had agents infused IV over 9 days; some also had lung liquid drained over 20 days. All had blood samples taken, lung liquid drained, then killed. |
|  |  | **USE OF ANAESTHESIA** | **HOW MOTHERS KILLED** | **HOW FOETUSES KILLED** | **WHEN FOETUSES KILLED** |  |
| **56 studies (but three studies report more than one experiment)** |  | **37 studies reported anaesthesia for CS delivery; 13 did not report anaesthesia for CS; in 5 studies mother was killed prior to CS; 1 study reported just sedation for CS and 1 reported stretching the rabbit and covering its eyes instead of anaesthesia\***  **Anaesthesia reported for other procedures to mothers in 13 studies (e.g. hysterotomy, foetal injections), but not in 11 studies where similar procedures conducted on mothers.**  **Anaesthesia reported for foetus/ neonate in 18 studies; anaesthesia not reported in 25 studies where animals survived for period after delivery, including 2 studies in which a paralytic agent was used.**    **Use of anaesthesia for either mother or foetus/ neonate not reported = 12**  ***\* There could be more than one procedure requiring anaesthetic in each study*** | **Mothers killed in 11 studies (prior to delivery = 7; after or around delivery = 4)**  **Manner of death to mothers: not reported 3; pentobarbitone 4; decapitation 2; thoracotomy 1; diethyl ether 1**  **In one study mothers (baboons) released back to gang cages after 4 weeks**  **Fate of mothers not reported in 44 studies** | **Foetuses killed with pentobarbitone to foetus 11; pentobarbitone and trachea clamped 10; left to die in/ out of uterus 6; lidocaine 5; trachea clamped 4; lidocaine and endotracheal tube plugged 3; decapitation 3; knot around neck 2; thiopental and string around neck 2; pentobarbitone to mother 1; pentobarbitone and rubber glove over head 1; thiopental and trachea clamped 1; severing cervical cord 2; endotracheal tube clamped 1; phenobarbital 1; not reported 10.**  ***NB: a single study could use more than one method for killing foetuses*** | **In utero = 2 ; At delivery 22**  **After tracheostomy at delivery = 1; After ventilation (after 15 mins ventilation = 3; 30 mins = 6; 40 mins = 8; 50 mins = 1; 60 mins = 3; 1.25 hr = 1; 2hrs = 2; 3 hrs = 2; 4 hrs = 3; 24 hrs =1); After breathing 5-30 mins = 1; between 10-120 mins age = 1; between 2-5 hours of age = 1; At 6 hours of age = 1; At 1 day of age = 4; At 2 days of age = 1; at 3 days of age = 1; at 5 days of age = 1; at 6 days of age = 1; not killed, observed until stopped breathing = 4; Not reported = 4**  ***NB: a single study could kill groups of foetuses at different time points*** |  |

**Table C: Antenatal corticosteroids: unexpected deaths, events, painkillers, paralytics, welfare**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study ID** | **Unexpected deaths** | **Unexpected events** | **Painkillers** | **Paralytic** | **Welfare** |
| 157 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Rats housed in a room with controlled temperature, humidity and lighting (0600–1800 h), and were given free access to food and water. |
| 158 | one to four abortions within treatment groups with higher doses | Nothing reported | Nothing reported | Nothing reported | Animals allowed to freely feed in paddocks between injections given at 7-day intervals. Animals undisturbed except for injections. |
| 159 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 160 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 161 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 162 | Foetal mortality in all groups but higher in groups that had T3 | Nothing reported | Nothing reported | Nothing reported | Rabbits housed individually and allowed to drink water and eat rabbit chow ad libitum |
| 163 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 164 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 165 | Nothing reported | Some animals having mechanical ventilation suffered pneumothorax | Nothing reported | Foetuses were given 0.2 mg pancuroniurn bromide (IP injection) | Nothing reported |
| 166 | 9 dead fetuses or fetuses too small for tracheal  cannulas | 8 suffered pneumothorax | Nothing reported | pups were paralyzed immediately after delivery with 0.1 mg of intra-abdominal  pancuronium. | Rabbits were fed carrots and cabbages during the last 2 days of pregnancy. |
| 167 | 6 fetuses dead.  About 50-60 abortions | 6 pneumothorax before 30 min of age. | Nothing reported | Nothing reported | Nothing reported |
| 168 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 169 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 170 | 6 abortions.  6 early fetal deaths | Nothing reported | Nothing reported | Each lamb received pentobarbital slow arterial infusion. No spontaneous respirations were noted for the remainder of the study. | Animals allowed to freely feed in paddocks between injections. Animals not handled other than for betamethasone or saline treatments. |
| 171 | 29 abortions  3 'fetal deaths' | Nothing reported | Nothing reported | lambs received supplemental pentobarbital if spontaneous respirations were noted | Nothing reported |
| 172 | 5 stillborn | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 173 | Nothing reported | Nothing reported | Analgesia for mothers  was supplemented with local infiltration of the incision site with xylocaine. | Each preterm monkey received  an injection of pancuronium bromide, 0.05  mg/kg. | Pregnant females were bred and maintained at the University of Washington Regional Primate Research Center Field Station. No dam was bred more than once for this experiment, and the infants were sired by a total of 9 males. Dams were flown to Seattle at 110 to 115 days of gestation and maintained in individual cages until CS delivery. |
| 174 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 175 | Nothing reported | Upon delivery 4 sheep found not to be pregnant | Nothing reported | Nothing reported | Nothing reported |
| 176 | 27 in utero  12 stillborn | Some foetuses oedematous in 7 litters | Nothing reported | Nothing reported | The does were mated with a buck for 1 to 2 hours and  then kept in individual cages |
| 177 | Nothing reported | Nothing reported | Nothing reported | Supplemental pentobarbital was administered if required to suppress spontaneous respiration | Nothing reported |
| 178 | ‘Foetal losses’ reported but figure unknown  Two does aborted all conceptuses. | One premature spontaneous  delivery | Nothing reported | Nothing reported | Rabbits housed in individual cages within same environmentally controlled room. Fed a standard diet. |
| 179 | The fetal mortality rate increased as the corticosteroid dose increased. Number unknown | Oedematous foetuses  11 pneumothoraces | Nothing reported | Nothing reported | Nothing reported |
| 180 | 1 dead foetus. Increased stillbirths some treatment groups. Number unknown | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 181 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 182 | 131 aborted or stillborn | 13 pneumothoraces; 7 upper airway leaks during placement of tracheal tube.  Some premature births | Nothing reported | Nothing reported | Nothing reported |
| 183 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | In some protocols animals not handled except for injections. |
| 184 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 185 | Postnatal deaths but not unexpected | 6 out of 17 mothers had spontaneous premature delivery | Nothing reported | Nothing reported | Nothing reported |
| 186 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 187 | 8 calves died during the 'experimental period' (first 24 hours of life?): 'various degrees of pulmonary hyaline membranes, atelectasis (collapsed lung), pulmonary and extra-pulmonary intravascular coagulation and systemic and CNS haemorrhages found at necropsy. | Nothing reported | Nothing reported | Nothing reported | Cattle were housed in 'tie stalls' on straw and were fed concentrates and hay twice daily with water available ad libitum. All cattle were healthy at the beginning of the study. |
| 188 | 5 (3 ewes aborted, 2 ewes carrying dead foetuses) | Pulmonary interstitial emphysema and lung rupture. PIE was present in up to one third of lambs in the treatment groups. Rupture of the lungs during inflation to 40  cmH2O pressure occurred in a few lambs in treatment groups. One lamb died after delivery despite maximal ventilatory support. | Nothing reported | Nothing reported | Nothing reported |
| 189 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 190 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | The rats were maintained on standard laboratory chow and water ad libitum and they were kept on a cycle of 12 hours of light /12 hours of darkness. |
| 191 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Pregnant rats and those with litters were caged individually with food and water freely available |
| 192 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 193 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 194 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 195 | Nothing reported | Nothing reported | Nothing reported | Spontaneous respiration was prevented with anaesthesia | Nothing reported |
| 196 | Nothing reported | Nothing reported | Nothing reported |  | Does kept in individual cages after mating. |
| 197 | 14 foetuses dead or macerated  at delivery. | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 198 | 4 deaths | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 199 | Nothing reported | Data from 1 steroid-treated-animal were not obtained because of technical reasons …'. Premature labour occurred where massive dosages of hydrocortisone were given and such treated foetuses had massive oedema. | Nothing reported | Nothing reported | Nothing reported |
| 200 | 7 lambs died in utero. | Nothing reported | Nothing reported | Pancuromium bromide as a 'muscle relaxant' | Nothing reported |
| 201 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 202 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 203 | 3 foetuses died | Nothing reported | Nothing reported | Although the preterm lambs were not paralyzed,  the level of anesthesia was sufficient to block spontaneous breathing during mechanical ventilation | Nothing reported |
| 204 | Nothing reported | Some high dose lambs had severe pulmonary interstitial emphysema. | Nothing reported | Although  the preterm lambs were not paralyzed, the level of anaesthesia  was sufficient to block spontaneous breathing  during mechanical ventilation | The ewes were easy to handle and not overtly stressed for the very brief treatment period, and they experienced no known stress in the 2 weeks before study. |
| 205 | 2 lambs died within 30 mins of delivery despite efforts to ventilate them. One ewe appears not to have survived the pre-delivery foetal procedures | One ewe delivered prematurely. | Nothing reported | Nothing reported | Nothing reported |
| 206 | Nothing reported | Nothing reported | Nothing reported | Each lamb received IM ketamine and acepromazine to prevent  spontaneous breathing | Nothing reported |
| 207 | Nothing reported | Nothing reported | Nothing reported | Each lamb received IM ketamine and acepromazine to prevent  spontaneous breathing | Nothing reported |
| 208 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 209 | Nothing reported | 6 animals had pulmonary interstitial emphysema | Nothing reported | Each lamb  Had pentobarbital by slow arterial infusion. No spontaneous respirations were noted for the remainder of the study. | Nothing reported |
| 210 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | Nothing reported |
| 211 | Nothing reported | Nothing reported | Nothing reported | Nothing reported | ‘After delivery of the foetus and repair of the maternal incisions, recovery of the female baboons was monitored daily for 2 weeks, with all animals released to outside gang cages after 4 wk.' Authors note that ultrasound examinations may have been sufficient to evoke a stress response in both groups. They also suggest there may have been chronic foetal stress. |
| 212 | Nothing reported | Nothing reported | Nothing reported |  | Nothing reported |
| **56 studies** | **Abortions/ dead or macerated in utero/ stillbirths / early foetal and postnatal deaths reported in 20/56 studies, but these cannot truly be described as unexpected. 36/56 reported nothing.** | **In 15/56 studies: pneumothorax (38 animals)/ upper airway leaks during placement of tracheal tube (7 animals) / mothers not pregnant / oedematous foetuses / premature delivery / PIE**  **41/56 nothing reported.** | **1/ 56** | **4/56 paralytic agent reported**  **9/56 report suppression of spontaneous breathing with anaesthesia** | **41 nothing reported.**  **15 reported (3 noted that animal handling minimal; 11 noted detail re animal housing or whether kept outside; 3 noted environmentally controlled room; 9 noted detail re food and/ or water; 3 noted details re mating; 1 noted animals’ transport to research centre; 2 made comment on animal stress; 1 reported post-operative care of mothers** |

**Table D: Antenatal corticosteroids procedures**

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| **Study ID** | **Procedures** |
| 157 | Dexamethasone administered to the pregnant rats on gestational days 17 and 18 (group A), 19 and 20 (group B), or 21 and 22 (group C). We’re not told how the drugs were delivered. Control groups were administered equivalent volumes of corn oil on the same three 2-d periods. In groups A and B, foetuses were delivered by CS (no detail on surgery) 1 d after the last drug treatment. Group C, rats delivered vaginally on gestational day 22. |
| 158 | PROTOCOL A: Ewes had ultrasound at 60 days gestation. Treated with Depo-Provera at 101 days gestation to avoid preterm labour / abortion. At 104 days ewes randomized to receive IM saline betamethasone injection. Some received one dose, some two, three and four doses. A control group received four weekly injections of saline (presumably IM, not told). All foetuses delivered by CS at 125 days gestation.  PROTOCOL B: Ewes randomized into one of four maternal treatment groups: IM betamethasone at 123 days gestation; and at 123 and 124 days gestation; intra-amniotic injection betamethasone at 123 days gestation; saline injection either IM or intra-amniotically. All foetuses delivered at 125 days gestation.  Comparison: For comparison, lung tissue and lavage fluid were collected from *eight near-term, untreated new-born lambs of 144–145 days gestation*.  Both protocols: at 125 days gestation ewes sedated and foetuses delivered by CS. The new-born lambs were mechanically ventilated. |
| 159 | 4 mothers had CS at day 24 gestation  11 mothers injected with betamethasone 24 and 48 h before CS delivery at day 26;  8 mothers injected with saline 24 and 48 h before CS delivery at day 26.  Each foetus was removed singly within the gestational sac and killed. |
| 160 | Group 1 mothers had IM isotonic saline daily for 3 days before preterm delivery. Group 2 mothers had betamethasone phosphate and betamethasone acetate IM daily for 3 days before preterm delivery. Delivery was by CS at various days of gestation. Amniotic fluid samples were obtained before delivery. |
| 161 | Prenatal ultrasounds performed at days 70 and 100. At 123 d of gestation pregnant baboons were randomly assigned to receive IM betamethasone or saline injections 48 and 24 h before delivery. For delivery pregnant baboons were intubated and foetuses delivered by CS at 125 d gestation. (Normal gestation 180 days.)  Foetuses were intubated and received surfactant by tracheal instillation. They received IV fluids but were not fed. Had constant IV infusion of glucose for 24 h, starting immediately after birth. Arterial blood (0.5 ml) was drawn at 0, 12, 18, and 24 h. Tracheal aspirates were obtained every 12 h during the study period of 6 d. Five days after birth, the baboons had an intravenous bolus of radioactive palmitate. |
| 162 | On day 25 and 26 of pregnancy, does were injected IM with either T3, betamethasone, both, or the appropriate amount of vehicle. Arterial blood was collected. Does were then killed on day 27 of pregnancy. The uterus was exposed. Some foetuses were injected with IM pentobarbitone through the uterine wall. These were used for a pressure-volume hysteresis experiment (no details given). Other foetuses were delivered. The amniotic sac was removed, umbilical cord was tied and these foetuses allowed to breathe until they died ‘naturally’. The remaining foetuses were delivered and decapitated immediately. |
| 163 | Does were injected IM with either betamethasone, T3, both, or vehicle, on days 24 and 25 of gestation. On day 26 does were anaesthetised and the foetuses delivered one at a time, at which time they were killed. |
| 164 | At 132 days gestation pregnant rhesus monkeys injected IM with varying doses of dexamethasone or vehicle, as either a single bolus injection or as four separate injections 12h apart. Before and after treatment maternal blood samples were taken. All maternal treatments commenced 72h prior to delivery. All foetuses were delivered by CS at around 135 days' gestation (usual gestation is 165 days). Prior to CS a maternal blood sample was collected. The umbilical cord was 'exteriorised' while the foetus was in utero and a blood sample was taken. |
| 165 | Does were injected 48 and 24 h prior to delivery with lactated Ringer's solution or betamethasone. At 27 days they were anesthetized, an endotracheal tube was placed via a tracheotomy and mechanical ventilation was initiated. Some foetuses were killed at birth, prior to first breath and underwent an alveolar lavage. Another group of foetuses was killed at birth for another set of experiments. A third group of foetuses had mechanical ventilation: Endotracheal tubes were placed via a tracheotomy. Each foetus was injected with either vehicle or surfactant prior to the first breath. Foetuses were connected to a ventilator, given pancuronium bromide and then sealed in an individual plethysmograph. |
| 166 | Does given betamethasone or vehicle IM on days 25 and 26 of gestation. Delivery was on day 27 by CS.  The pups were weighed and paralyzed immediately after delivery with intra-abdominal pancuronium. The trachea was isolated and a metal cannula was inserted through the larynx, slightly distended the tracheas of the smaller animals. Half of the foetuses from each litter were given rabbit surfactant before the first breath and half were given vehicle, by direct intra-tracheal injection. The chest and abdomen were pressed before treatment to allow the lung liquor to rise into the endotracheal tube. There were four groups of foetuses: control, corticosteroid-treated, surfactant-treated, and combination-treated. Each pup was placed in its own plethysmograph, which was heated to 37”. Pups were ventilated. Before pulmonary function measurements, foetuses were transferred to a separate plethysmograph chamber and given three breaths at a higher ventilator pressure. Each breath consisted of a complete inspiration and expiration followed by an inspiration and a clamping just before end inspiration. The ventilator tubing was then quickly removed and the animal was allowed to freely exhale. Each measurement repeated three times. After 1h animals killed. Another group of pregnant does was treated as above with either steroids or vehicle and delivered on day 27. Foetuses from does were weighed and killed at birth. |
| 167 | Rabbits had IM betamethasone on gestational days 25 and 26, (term is 28-35 days) 48h and 24h before delivery on day 27. Other rabbits had vehicle injections only. A second group had IM betamethasone and IV dexamethasone 4h before delivery.  Delivery: Foetal rabbits were sequentially removed and weighed, and a tube tied into the trachea of each rabbit via a neck incision. Alternate rabbits received saline containing albumin, or saline containing albumin plus surfactant. The tracheal tube of each rabbit was connected to an anaesthesia bag delivering 100% oxygen and the rabbit ventilated for about 5 breaths until satisfactory chest motion occurred, after which it was transferred to a ventilator. The rabbit received IV albumin in saline via external jugular vein. |
| 168 | Pregnant rabbits were given IM betamethasone 48 and 24h before preterm delivery at 27, 28, and 29 days gestation or before term delivery at 31 days. Control does at each gestation receive injections with vehicle at the same times. The foetuses were sequentially delivered. The trachea of each was exposed through a small incision in the anterior neck, and a short tube tied into the trachea. Alternately delivered foetuses then received, via the endotracheal tube, either saline containing albumin or saline containing the albumin plus surfactant. Each rabbit was ventilated with 100% oxygen using an anaesthesia bag and manometer for about five breaths and transferred to a ventilator-plethysmograph system. Three litters of the 31-day gestation rabbits delivered spontaneously 1 to 3h before being studied and the other litters were delivered by CS and allowed to breathe for 1 to 2 h before being studied. Immediately after the start of mechanical ventilation, each  rabbit received saline containing albumin via the external jugular vein. |
| 169 | Mothers given betamethasone or vehicle 24 and 48h before delivery at 27 days. In multi-hormone protocol does given betamethasone or T3 at 24 and 48h before delivery at 27 days. Intravenous TRH or saline was given at 12, 24, 36 and 48h before delivery at 27 days. Some had TRH and betamethasone, or T3 and betamethasone. Foetuses were sequentially delivered by CS, weighed and a tube secured in the trachea through an anterior neck incision. Via the tracheal tube each new-born rabbit had saline or saline containing surfactant. Each rabbit ventilated with 100% oxygen using an anaesthesia bag and manometer for about 5 breaths before being transferred to a ventilator. Immediately after placement on the ventilator each rabbit had an injection of saline containing albumin via one of the external jugular veins. |
| 170 | Ewes given IM medroxyprogesterone at 101 d gestation, to minimize preterm labour and abortion. At 104, 111, 118 and 124 days gestation, ewes had either IM saline or betamethasone. At 125 days (term is 152) ewes had operation to deliver lambs by CS. During this operation the foetal head was exposed, a tracheotomy performed and an endotracheal tube tied into place. The foetus was then delivered. An arterial blood sample was drawn from the placental cord. After delivery the lamb was dried, ventilated, an arterial catheter advanced into the descending aorta through an umbilical artery and each lamb received pentobarbital by slow arterial infusion. No spontaneous respirations were noted for the remainder of the study. The body temperature of each lamb was maintained. A final arterial blood sample was taken. |
| 171 | Ewes had one or three doses (at 7-day intervals) of IM betamethasone and/ or saline three times prior to delivery which could be at either 125, 135, or 146 days’ gestation. Ewes in all protocols were weighed and received injections of Depo Provera. For some protocols the foetus rather than the ewe had one or three doses of betamethasone, or saline and betamethasone. At delivery the foetal head was exposed and the foetus was sedated and its neck anesthetized. After tracheotomy, an endotracheal tube was securely tied into place.  Each foetus was then delivered, and an arterial blood sample was drawn. After delivery, the lambs were dried and ventilated with time-cycled, pressure-limited infant ventilators. An arterial catheter was advanced into the descending aorta through an umbilical artery, and lambs received supplemental pentobarbital (15 mg/kg) by slow arterial infusion if spontaneous respirations were noted. The body temperature of each lamb was maintained at 39°C. A final arterial blood sample was taken. |
| 172 | Some mothers injected s.c. with betamethasone or saline 1 day before delivery and some on 2 consecutive days before delivery. Pups delivered by CS the day after the injection(s). |
| 173 | Mothers received either IM saline or dexamethasone 1, 2 or 3 days before CS delivery at 135 days gestation. (term = 183) For delivery mothers anaesthetised and ventilated. A sample of venous blood, a sample of amniotic fluid, a sample of blood from the umbilical vein and a sample of cord blood were obtained. Each infant monkey was resuscitated as necessary with intubation and ventilation using 100% oxygen until effective spontaneous respirations were established. A rectal temperature probe was inserted and core temperature was maintained. Once stabilised, umbilical arterial and venous catheters were inserted and Dextrose infused through the arterial catheter. A tracheostomy was performed under local anaesthesia, and the animal was mechanically ventilated using a small animal respirator and monitored continuously. Each preterm monkey had an injection of pancuronium bromide. At 2 h of age palmitate, then unlabelled palmitate, was infused through the venous catheter. At 2.5 h, a chest radiograph was obtained. At 3 h, blood samples were obtained. The animal was then killed. |
| 174 | Mothers had IM saline or betamethasone phosphate and betamethasone acetate daily for 3 days or 13 days prior to CS delivery at 132 days’ gestational age (term is 160-165). Foetuses were killed upon delivery. |
| 175 | All ewes received IM medroxyprogesterone once and antibiotics every day until delivery (unclear when antibiotics started or how delivered). At 122 days gestation pregnant ewes had arterial and venous catheters placed in femoral vessels under anaesthesia (procedures lasted less than 20 minutes). Ewes had either IV vehicle every 8 hours for 2 days; IM betamethasone daily for two days; IV TRH over 30 mins every 8 hours for 2 days; IM betamethasone daily for two days, plus IV TRH over 30 mins every 8 hours for 2 days. Blood samples were taken daily. On day 125 gestation foetuses were delivered by CS. |
| 176 | 2 series of experiments: 1. Cortisol or saline injected IM into pregnant rabbits for 3 days before delivery. 2. Two to 3 days prior to premature delivery, pregnant mothers had laparotomies and either cortisol or saline injected directly into foetus and amniotic sacs through uterine wall. Surgery took average of 15 mins, with does fully awake and returned to cages within 30 minutes of surgery. The foetuses were delivered by CS between 26 - 29 days’ gestation. Some foetuses were killed before the first breath. Other new-born rabbits were kept warm and observed for 15 to 20 min (and in some cases up to 2 hours). At 26 days both control and treated rabbits gasped poorly and in most the lungs were completely collapsed or poorly aerated. |
| 177 | Each ewe had medroxyprogesterone 4 days prior to commencement of protocol. 3 weeks prior to CS delivery, ewes had weekly IM injections of either saline, a single dose of betamethasone and two saline injections, or three weekly injections of betamethasone, then delivery at either 125, 135 or 146 days (term is 150 days). Delivery went to term in a further group of ewes that had three weekly IM injections of saline commencing at 104 days. At CS delivery a midline abdominal and uterine incision was made to ‘deliver’ the foetal head. The foetus was sedated and locally anaesthetised. Following tracheotomy, an endo-tracheal tube was secured and the foetus was delivered. Lambs were weighed and commenced on ventilators. An umbilical arterial line was positioned and supplemental pentobarbital was administered if required to suppress spontaneous respiration. Lambs were kept warm. After measurements were performed lambs were killed. |
| 178 | Rabbits were either handled but not given injections, had saline only, or 1, 2, or 3 courses of betamethasone beginning day 19, or 1 or 2 late courses. (Route of drug administration not reported) All does were killed on gestational day 27 and uteri removed and immediately opened. Foetuses and placentas were weighed. The numbers of live born and stillborn foetuses were noted. Authors do not state how or when foetuses died or whether they began subsequent procedures (such as collecting blood) before or after their deaths. |
| 179 | Rabbits were weighed and injected  IM with saline or various doses of betamethasone 48 and 24 hours before delivery on day 27. Foetuses were delivered by CS. On delivery, rabbits used for foetal wash, ventilation, or pressure-volume measurements had IP anaesthesia and were weighed. Then, a tracheostomy tube was tied into the trachea. After this some rabbits were killed straightaway with intrathecal lidocaine. Some were given five breaths of oxygen through the tracheal tube, ventilated for 30 mins, given IV saline containing albumin via the external jugular vein, then killed after 30 mins with an intrathecal injection of lidocaine. Some were placed on the ventilator and given 10 breaths, following which the tracheal tube was plugged for 5 minutes to collapse the lungs, then killed. |
| 180 | Rats were injected IM with dexamethasone, T3 in saline, the two hormones together, or just saline on the 2 days prior to killing on 17-22 days gestation. (Term is 22 days.) Dexamethasone was administered twice a day while T3 was injected only once a day. Some mothers were killed and the foetuses delivered by CS. Others gave birth spontaneously (on day 22) and the new-borns were kept with the mother for a day. Foetuses and new-borns were killed by decapitation. |
| 181 | Mothers had IM betamethasone or vehicle 48 hours, or 24 and 48 hours, before delivery. Mothers lightly anesthetized for CS delivery at 27 days. Preterm rabbits sequentially delivered and anaesthetised. A tracheal tube was tied into the trachea of each rabbit. Every other rabbit in each litter received natural sheep surfactant. Each rabbit was ventilated with five breaths of 100% O2 using an anaesthesia bag with just enough pressure to visibly move the chest. The rabbits then ventilated for 30 minutes. Immediately after initiation of ventilation rabbits given an external jugular vein injection of saline containing labelled albumin. |
| 183 | Ewes with singleton pregnancies identified by ultrasound at 60 days gestation and given Depo-Provera at 101 days gestation. 3 treatment protocols. Sheep injected IM with 1-4 doses betamethasone or saline either 15 hours, 48 hours, or weekly starting at 104 days gestation before preterm delivery, OR their foetuses had ultrasound-guided intra-amniotic or foetal IM injections at the assigned times. In Protocol A: drugs were given 15 h prior to delivery by CS at 123 days. In Protocol B drugs were given 48 h prior to delivery by CS at 125 days and foetuses received intratracheal beractant. In Protocol C drugs were given weekly starting at 104 days gestation and foetuses were delivered by CS at 125. Some lambs had 40 minutes of ventilation, others (96) had 4 hours of ventilation but no details at all on ventilation procedures. |
| 182 | Mothers had 1 - 4 injections at various times before delivery. Some had various doses of thyrotropin releasing hormone (IV) with betamethasone (IM); some had saline delivered IV and IM, some had saline (IV) combined with betamethasone (IM). On day 27 the mothers had CS delivery under light anaesthesia. New-born rabbits had IP anaesthesia then had a tracheal tube tied into the trachea. The chest was compressed and released as either albumin or surfactant was injected through the trachea into alternate foetuses from each litter. After this injection approx. 5 breaths of 100% oxygen was given with an anaesthesia bag and manometer to initiate ventilation. The rabbits were then transferred to ventilation systems, immediately after which each rabbit was given albumin via the external jugular vein. They were ventilated for 30 mins then killed. |
| 184 | Beginning on day 24 gestation, mothers injected IM with saline or hydrocortisone phosphate every 8 hours for 3 days. The weight of food consumed by the animals was recorded each morning. On day 27 mothers anesthetized and killed during thoracotomy and foetuses removed rapidly from the amniotic sac. Foetuses’ tracheas were clamped immediately to prevent respiration. After measuring weight of each fetus, the animal was then exsanguinated by cutting through the abdomen. The lungs and liver were removed. |
| 185 | Mothers had betamethasone or saline on days 26 and 27 gestation. On day 29 pups were delivered by CS. Pups were allowed 0, 6, 24, or 48 hours of breathing air. Those in the 0 hours group were left in amniotic sacs to prevent breathing. At 6h all pups were given a dextrose / saline solution by clysis (large injection of fluids). Gavage fluids (artificial milk by nasogastric tube) were given every 24 h. Some foetuses had their lungs metabolically 'degased' by putting them in 100% oxygen as soon as they had anaesthesia (for killing). |
| 186 | **Protocol 1**: All ewes were weighed and had IM medroxyprogesterone at day 98. Beginning on day 104 each ewe either had 3 IM injections at 7 day intervals, or their foetuses had IM injections by ultrasound guided injection. (The injections were either 3 doses of betamethasone, 2 doses saline and 1 betamethasone, or 3 saline). All animals were delivered on day 125.  **Protocol 2:** All ewes were weighed at day 98 and had medroxyprogesterone at day 108. Mother had either IM betamethasone at days 114, 121 and 128, betamethasone at day 114 and saline at days 121 and 128, or saline at each time point. **Protocol 3:** Ewes had three doses IM of either betamethasone or saline at days 104, 111, and 118. Foetuses were delivered by CS on day 125, 135, or 146. (Term = 150 d). They were mechanically ventilated for 40 minutes. |
| 187 | Experiments started between days 258-270 gestation (term is 284). Cows had laparotomies. Part of the pregnant uterine horn with the hind legs of the calf was 'exteriorised' and a sterile catheter and needle advanced through the intact uterine wall into the amniotic cavity to collect 1-200 ml amniotic fluid. The uterus was then repositioned and the surgical wound repaired. 12 hours later some cows had IM injections of glucocorticoid flumethasone, some had IM dinoprost and some saline. 30 hours after the injections all cows had CS delivery in standing position under local anaesthesia. Amniotic fluid was again collected. Blood samples were taken from cows 3 times. Blood samples were taken from calves during CS (via an umbilical artery) and at 1, 6 and 24 hours after birth (from a jugular vein). Calves were observed for signs of respiratory distress and 14 calves were found to have RD. |
| 188 | All mothers had IM medroxy-progesterone then they had either saline or betamethasone  injections into rump, or single intra-amniotic injections of saline, betamethasone or budesonide on either 2 or 7 days before delivery. For intra-amniotic injections ewes were restrained in a position similar to that used for shearing to allow ultrasound imaging of the foetal heart and fluid surrounding the foetus. After sterilization of the maternal abdomen a spinal needle was used to aspirate 2ml fluid before injection. Ewes were returned to a field after treatment. Two or 7 days after treatment (123-125 days gestation) preterm lambs were delivered by CS. The foetal head was delivered and, after insertion of an endotracheal tube by tracheostomy, lung fluid was aspirated prior to delivery. An umbilical arterial blood sample was withdrawn from the placental cord. Lambs were dried and ventilated for 40 minutes. A catheter was advanced into the descending aorta through an umbilical artery for pentobarbitone anaesthesia and for withdrawal of arterial blood samples at 10-minute intervals. At 40 minutes of age lambs were killed. |
| 189 | Mother rats had IP injections of saline or one of three corticosteroids on day 20 gestation. Rats were killed on day 21. Four live foetuses were taken from each rat. The four pairs of foetal lungs from each rat were pooled and the lung tissue homogenised. |
| 190 | Main experiment: Mother rats had IP dexamethasone or saline 48 and 24 hours prior to delivery. Foetuses delivered at 19, 20, or 21 days by hysterotomy (incision in uterus) under anaesthesia. New-born rats delivered after normal parturition. Survival Studies: In two experiments, rats were delivered a day early (day 21 of the normal 22-day gestation period) by hysterotomy and transferred to a specially constructed warmed plastic-covered cage assembly sitting atop a gently shaking water bath. A flow of oxygen was provided at concentration of 35-40%. Survival times monitored at 10- to 15-minute intervals. |
| 191 | Mother rats were weighed at various ages or stages of pregnancy and injected IP with dexamethasone in dimethylsulfoxide or dimethylsulfoxide (vehicle) alone. Twenty-four hours later animals were decapitated and their lungs removed. The uteri from pregnant rats were removed with foetuses intact and placed in iced saline. Each foetus was separated from its placenta and umbilical cord and weighed, after which lungs removed. |
| 192 | Pregnant and new-born rats were injected IP with dexamethasone in dimethylsulfoxide or with dimethylsulfoxide alone 24 hours prior to death. Foetuses delivered on days 19 and 21 of gestation. New-born rats studied for either 1, 3 or 5 days. Mothers’ lungs studied as well as those of foetuses and new-borns. |
| 193 | Pregnant rats had IP placebo or betamethasone from days 16 - 18 of gestation. Foetuses delivered by CS on day 19 gestation. 5 untreated pregnant rats had foetuses delivered by CS, on day 20 gestation. Immediately after delivery the foetuses were killed. |
| 194 | Pregnant rats had agent or saline injected IP from day 17 gestation for 3 consecutive days. Rats killed on day 20. Foetuses delivered by rapid post-mortem hysterotomy, lungs removed. |
| 195 | Foetuses of sheep had a single ultrasound-guided IM injection of saline, betamethasone, or betamethasone plus thyroxine (T4) at 125 or 126 days gestation (term 152). Forty-eight hours later the foetuses were delivered by CS, mothers having been anaesthetised. Foetuses were anaesthetised and their heads and necks were exposed and the anterior neck anaesthetised. Endo-tracheal tubes were secured by tracheostomy, approximately 10 ml of foetal lung fluid was withdrawn and the endotracheal tube clamped. The lamb was delivered and weighed, then had a pulmonary surfactant preparation by intra-tracheal instillation. The lambs then were ventilated. A catheter was placed in the aorta via an umbilical artery. Lambs were given an infusion of dextrose. Spontaneous respiration was prevented by supplemental IM ketamine and acepromazine. Each lamb had albumin by injection via catheter at 2 hours of age and killed at 3 hours of age.  At 27 days gestation rabbits were given the surfactant recovered from the lambs. Rabbits were anaesthetized and foetuses delivered by CS. Foetuses weighed and anaesthetised. A tube was tied into the trachea of each rabbit and rabbits were given either pulmonary surfactant preparation, one of the surfactants recovered from the lambs, or nothing. The rabbits were ventilated for 15 minutes. |
| 196 | Rabbit mothers anesthetized with halothane or ether and given laparotomies. Cortisol was injected into the foetal abdomen and the amniotic sac. Foetuses were aged 19, 22, 24 and 25 days (term is 30) when injected. Foetuses delivered via hysterotomy 2 or 3 days after cortisol injection. Most foetuses were prevented from breathing by tying their necks immediately after delivery. Some were kept on a heating blanket, allowed to breathe, and observed from 10 minutes to 2 hours. |
| 197 | Pregnant rabbits were operated on at 26 days gestation under anaesthesia to expose the uterus and inject 2-4 foetuses IM through the intact uterine wall with hydrocortisone hemissuccinate and barium sulphate. On day 28 of gestation, the doe was stretched on its back, its eyes were covered, and traction applied to its neck and head to quieten it sufficiently for the incision to be reopened and foetuses removed, after which doe was killed. After delivery of each foetus it was placed in an observation box. Two minutes of apnoea was defined as time of death. No attempt was made to feed or resuscitate the new-born rabbits. New-born rabbits observed to see how long they survived for, up to 6 hours. |
| 198 | At gestational day 27.5 pregnant rabbits had their uteruses exposed by midline abdominal incision under anaesthesia. Each foetus had an IP injection of either aminophyllin, dexamethasone in saline, or saline alone. The abdominal incision was closed with a continuous suture and the doe allowed to recover. After 2.5 hours the abdomen was reopened under anaesthesia and the foetal rabbits delivered by hysterotomy. They were killed immediately. |
| 199 | Non-steroid treated group: Ewes had CS delivery under anaesthesia. Their foetuses had tracheostomies done while umbilical circulation still intact. A tube was secured into the trachea and tracheobronchial tree suction done. The umbilical cord was tied and animals were ventilated. Rectal temperature was monitored. An arterial catheter was placed in the aortic arch via an umbilical artery. The right external jugular vein was cannulated with a catheter through which contrast agent was injected. Some had two injections of contrast agent. The animals were killed between 2 and 5 hours of age.  Steroid treated group: Pregnant ewes underwent hysterotomy and the head of one of the foetuses was brought through the incision. A small incision was made through the amniotic membranes and skin and a catheter was placed into the external jugular vein, sutured into place and the membranes, uterus and abdomen closed. IV hydrocortisone was given every 8-12 hours for 4-14 days. Twin controls had no procedures. At CS delivery at 111 - 130 days, the treated foetuses were ventilated and studied by catheterization and angio-cardiography. The control twin breathed room air, was not ventilated. |
| 200 | Ewes undergoing general anaesthesia had trachea intubated and mechanical ventilation. All ewes had femoral artery catheters inserted. For those ewes whose lambs were to have hydrocortisone or placebo, an incision was made to expose the uterus and a foetal leg pulled out to permit catheterisation of foetal femoral artery and foetal peritoneal cavity. The leg was then replaced and the incision sewn up, with foetal catheters remaining on outside, coming through a subcutaneous flank incision. The ewes were allowed to recover and the lambs received IP injections of hydrocortisone or saline daily for 3-5 days. At the end of the treatment period the ewes were re-anaesthetised with IV pentathol and the lambs delivered by CS. The new-born lambs' tracheas were clamped immediately and they were killed with IV pentathol. Other ewes were anaesthetised and delivered lambs without treatment. These lambs were immediately killed with IV pentathol. |
| 201 | Some pregnant rabbits had IM ritodrine or saline at days 26-28 gestation. Others were operated on under local anaesthesia to give IM drugs to their foetuses (either betamethasone or saline) at the same time, while other foetuses had just IP ritodrine at delivery, or IP ritodrine at delivery in addition to earlier IM injections. Following injections, barium sulphate was injected IM to identify the drug-exposed foetuses by radiography after the experiment. One to two foetuses received the injection and the littermates served as controls. The foetuses were removed from the uterus by CS under local anaesthesia, and the umbilical cord was cut. The new-born animals were kept in room air at 25 °C, and were allowed to breathe for 5 or 30 minutes. |
| 202 | Ewes were operated on 123 - 127 days gestation (term is 148) under epidural anaesthesia. Catheters were placed in a foetal carotid artery, jugular vein, and in the trachea. The tracheal catheter was connected to a latex bag which was left in the uterus. A separate exit catheter from the bag was exteriorized through the ewe's flank together with the foetal artery and vein catheters. After the operation, mothers had antibiotics and were allowed to recover from the operation for 7 days. The foetuses had either nothing, cortisol infusion, TRH infusion, P-agonist infusion, cortisol plus P-agonist infusion, cortisol plus TRH infusion, or cortisol plus TRH plus P-agonist infusion. Agents infused IV. Arterial blood was taken from foetuses at three time points, the last being on day of death. Tracheal fluid collected daily. |
| 203 | At 121 days gestation pregnant ewes were given anaesthesia, the uterus was exposed, a hysterectomy was performed, and the hind limb artery and vein of each foetus were isolated.  Arterial and venous catheters were introduced and the wounds closed. The ewes were given antibiotics for 24 hours after surgery. Their foetuses subsequently had either saline, corticosteroid, TRH, or a combination of corticosteroid and TRH, all delivered by continuous IV infusion plus five intermittent bolus injections.  At 128 days gestation ewes were anesthetized and given a tracheostomy. Foetuses were delivered by CS. After the head and neck were exposed, foetuses received anaesthesia and an endotracheal tube was tied into the trachea via tracheostomy. Foetal lung fluid was removed with a syringe, and the endotracheal tube clamped. The umbilical cord was cut, body weight was measured, and the lamb dried. Venous cord blood was sampled. Some lambs had surfactant treatment while the other received sham via the endotracheal tube, and all received labelled albumin. Lambs were then ventilated. An umbilical artery catheter was placed through which animals were given albumin. Core body temperature was maintained. The level of anaesthesia was sufficient to block spontaneous breathing. After 1.25 h of ventilation, blood was collected and the lambs were killed. |
| 204 | Ewes had ultrasound at 50 days gestation. The lower anterior abdominal wall of each ewe was shorn and washed with ethanol. Foetal injection procedures were performed with the ewe in a sitting position, held from behind by a seated assistant. The foetus was imaged with ultrasound and the foetus was injected IM with betamethasone or saline. For foetuses receiving intravascular injections, the foetal heart was imaged and the spinal needle was advanced until it could be seen within the heart and blood was withdrawn. Hydrocortisone or saline was injected in a process that took about 5 minutes. Either 24 or 48 h after the foetal treatment, at 128 days gestation, preterm lambs delivered by CS. The foetal head was exposed through midline abdominal and uterine incisions. A tracheotomy was performed and an endotracheal tube tied into the trachea. Lambs were dried with towels and ventilated, avoiding peak pressures (to avoid pneumothorax). The lamb’s body temperature was maintained. An arterial catheter was passed via the umbilical artery into the aorta and glucose infused. After initiation of ventilation, each lamb had pentobarbital sodium to prevent spontaneous breathing during the 50-min study period. Blood drawn. |
| 205 | At 122-125 days gestation ewes were anaesthetised and a midline hysterotomy incision was made to expose the uterus. A foetal hind limb was pulled through the incision. Femoral arterial and venous catheters were placed. The second foetus underwent an identical procedure. The catheters were then 'exteriorised' and stored in a pouch on the ewe's flank. Postoperatively the ewes and foetuses received daily antibiotics for 3 days. Infusion of agents started 3-4 days later, on day 128 gestation: foetuses received either saline, corticosteroid, or corticosteroid plus TRH. All had a 60 hour infusion and 5 intravenous bolus injections 12 hours apart. At 130 days gestation foetuses were delivered by CS. The foetal head was 'exteriorised' through a small uterine incision and foetuses were anaesthetised. A tracheostomy was performed and an endotracheal tube secured. The right carotid artery was catheterised. The foetus was delivered and transferred to a warmer and placed on a ventilator. All animals were treated with natural surfactant by direct tracheal instillation. Blood samples were taken 6 times and replaced with maternal blood. Dextrose was infused. |
| 206 | Foetal treatments: The foetal heart and chest were imaged with ultrasound. The foetus was injected with either betamethasone or saline. Preterm lambs were delivered at 134-135 day by CS 48 hours after foetal treatments. After tracheostomy, an endotracheal tube was secured, foetal lung fluid was aspirated and the endotracheal tube clamped. A blood sample was drawn from the umbilical cord. The lamb was delivered, weighed, and ventilated. Each lamb had ketamine and acepromazine IM to prevent spontaneous breathing. A catheter was passed via an umbilical artery into the distal aorta. Body temperature was maintained and each lamb received a continuous infusion with dextrose via the arterial catheter. The animals also received filtered maternal blood for replacement of blood samples. After the 2 hour post-delivery study period, the lambs were killed.  Rabbits: Preterm rabbits at 27 days gestation were sequentially delivered, weighed, and anaesthetized. The trachea of each rabbit was cannulated, and surfactant from betamethasone or saline-treated lambs given via the tracheal tube, with an untreated control group. Each rabbit was ventilated for five breaths with an anaesthesia bag then ventilated for 15 minutes, after which the ET tube was plugged for 5 minutes. |
| 207 | At 126 or 127 days gestation ewes’ foetuses had ultrasonographically guided foetal injections of either IM betamethasone or IM saline, 8 or 15 hours before preterm delivery. Preterm lambs were delivered at 127 - 128 days gestation by CS. A tracheostomy was performed and an endotracheal tube placed in the trachea. A venous blood sample was drawn. The lamb was delivered, weighed, and ventilated. Each preterm lamb had IM ketamine and acepromazine to prevent spontaneous breathing. A catheter was passed through an umbilical artery into the distal aorta. Within 3 minutes of delivery each lamb was given labelled albumin intravascularly through this catheter. Body temperature was maintained and each lamb received a continuous infusion of dextrose through the arterial catheter. The animals also received filtered maternal blood for replacement of blood withdrawn for samples. |
| 208 | At 126 or 127 days gestation pregnant ewes and their foetuses had either: maternal saline and foetal saline, maternal betamethasone (12 mg) and foetal saline, maternal betamethasone (0.5 mg) and foetal saline, maternal saline and foetal betamethasone (0.2 mg), or maternal saline and foetal betamethasone (0.5 mg). Foetal treatment given by ultrasound-guided IM injection. Each ewe was sedated and anaesthetized 24 hours after foetal or maternal treatment. An incision was made to expose the foetal head and neck and the foetus was sedated and anesthetized. After tracheostomy, an endotracheal tube was tied into the trachea. Foetal lung fluid was withdrawn, and the tracheal tube clamped. Each lamb was weighed and had Survanta (for RDS). The lambs were ventilated. A catheter was advanced into the aorta via an umbilical artery, and frequent blood samples were obtained. Filtered cord blood was given, as well as a constant infusion of dextrose. Blood pressure was recorded and rectal temperature monitored. The lambs were given a 20 minute hypoxic challenge at 3 hours of age by reducing the oxygen concentration with nitrogen. At 3.5 hours of age, each animal received albumin via the arterial catheter, and 30 min later a final blood sample was obtained. After 4 hours ventilation, the lambs were killed. Rabbits: surfactant function was tested in 27 day preterm rabbits. A tube was secured into the trachea and each rabbit received a surfactant via trachea, with 1 rabbit in each litter being an untreated control. After lung inflation with 100% oxygen, rabbits were transferred to a ventilator and ventilated for 15 minutes, after which tracheal tube plugged for 5 minutes to allow absorption of oxygen and animals killed. |
| 209 | At 121 days gestation the foetuses of ewes had betamethasone or saline by IM injection. Six days later they had a second dose of either betamethasone or saline again IM. One day after the second dose (at 128 days' gestation), the ewes delivered lambs under anaesthesia. The foetal head was exposed and the foetus was sedated. The anterior foetal neck was anaesthetized and after tracheotomy an endotracheal tube was secured. The foetus was then delivered a blood sample drawn from the placental cord. After delivery the lamb was dried and ventilated. The body temperature of each lamb was maintained at 39°C. An arterial catheter was placed and dextrose was infused, as well as pentobarbital to prevent spontaneous respiration. After a final blood sample lambs were killed. |
| 210 | At 122 days gestation ewes and foetuses had either ultrasound-guided IM foetal injection of betamethasone plus maternal saline injections, maternal betamethasone and foetal saline injection, or foetal and maternal saline injections. Preterm lambs were delivered by CS at 123 days gestation. Each ewe was sedated and anaesthetised. The foetal head was exteriorized and the foetus had sedation and local anaesthesia. A tracheal tube tied into the trachea. Tracheal fluid was aspirated and the endotracheal tube clamped. After delivery, the lambs were weighed and treated with Survanta (surfactant) while being rotated through 4 positions. Animals were ventilated for 4 hours. Body temperature was maintained. After initiation of ventilation, a catheter was placed into the aorta and filtered cord blood was given, blood samples taken, arterial pressure recorded and dextrose administered. A second catheter was placed into the left ventricle for administration of radiolabeled microspheres. These were injected at 2.5 hours and a reference sample withdrawn from the aortic catheter. |
| 211 | Amniocentesis was performed under ultrasound at 70 days gestation to identify male foetuses. At 124 days (term is 185 days), the foetuses were again imaged using ultrasound. The foetus of each baboon had either betamethasone or saline injected IM under ultrasound. The female baboon was then returned to her cage. 24 hour later the mothers had CS to deliver their foetuses. The new-born foetuses were intubated using endo-tracheal tubes. They had surfactant by tracheal instillation and ventilation was initiated. The new-born baboons were kept sedated. An arterial catheter was placed into the descending aorta for blood pressure monitoring and blood gas sampling. A deep venous catheter was placed into the inferior vena cava for administration of fluids and drugs. All animals received a single IV injection of inulin. They were not fed. They were given parenteral fluids containing amino acids and multivitamins. IV fluids were administered and IV antibiotics were given. Arterial blood samples and blood samples from the umbilical cord were taken up to six times. A plasma sample was collected 30 minutes after delivery. Blood samples were replaced with heparinized adult baboon blood. Animals were monitored with an electro-cardiogram and cardio-respiratory monitor. At 22 hours, each new-born received an intra-vascular injection of labelled albumin and after 24 hours of ventilation, baboons were deeply anaesthetised, ventilated for 2 minutes with 100% O2 and then killed. |
| 212 | Surgery was performed on pregnant ewes and their foetuses at 109 days gestation (term 147 days) to implant foetal and maternal vascular catheters and bi-directional foetal tracheal catheters. After the recovery period, lung liquid was drained using the descending tracheal catheter. 5 days was allowed for animals to recover from surgery before experimentation. Measurements of foetal arterial blood were made every second day. Foetuses had either: IV saline infused into foetus for 9 day, IV cortisol infused into foetus at increasing doses for 9 days, foetal lung liquid drained by gravity into a sterile bag for 20 days and IV saline infusion to foetuses for 9 days, or foetal lung liquid drained by gravity into a sterile bag for 20 days and IV cortisol infusion to foetuses for 9 days. Foetal blood samples were collected every 2–3 days. All infusions continued until death at 131 days. Just before death the foetal lungs were drained via the descending tracheal catheter. |

**Table E: Antenatal corticosteroids: models**

**Non-ventilation models**

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| **1.1 MATERNAL DRUG ADMINISTRATION AND FOETUSES KILLED AT DELIVERY (Rats, monkeys, rabbits, sheep)** | **STUDIES** |
| In this model pregnant mothers are given drugs (either IM, S/C, IV via catheter or IP) prior to delivery for a number of days (usually 2-3 days, but can be as many as 13 days). Some mothers may be given progesterone. The mothers are then given Caesarean Sections to deliver their babies preterm, usually under anaesthesia. Some pregnant mothers might have CS delivery without prior injections. Additional procedures could include being given antibiotics or having blood samples taken. Most mothers then have their foetuses/ new-borns taken away. Some mothers are killed after delivery or more commonly prior to delivery using a variety of methods (including pentobarbital, decapitation, pentobarbital and thoracotomy and inhalation of diethyl ether). The fate of most mothers after CS is unreported.  Most studies of this type do not involve procedures to foetuses although some may have blood taken in utero. Most foetuses are killed at pre-term delivery using a variety of methods (including tracheal clamping, tracheal clamping and thoracotomy/ exsanguination, pentobarbital, thiopental, strangulation, pentobarbital and suffocation, decapitation). Some foetuses are left to die in utero and some are delivered and left to die. | 160, 163, 172, 174, 175, 178, 162, 164, 159, 184, 189, 190, 191, 193, 194 |
| **1.2. MATERNAL DRUG ADMINISTRATION AND FOETUSES KILLED > 1 DAY AFTER DELIVERY (Rats)** | **STUDIES** |
| In this model pregnant mothers are given drugs (either IP or IM), then are either killed (decapitation after concussion) or deliver their foetuses preterm by Caesarean Section under anaesthesia, or by vaginal birth at term. Their foetuses are either taken away at delivery or one day later.  The foetuses are delivered pre-term or at term either killed at delivery (decapitation) or observed for 1, 3, or 5 days. | 192, 157, 180 |

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| **2. 1 MATERNAL DRUG ADMINISTRATION AND FOETAL DRUG ADMINISTRATION, FOETUSES KILLED SOON AFTER DELIVERY (Rabbits)** | **STUDIES** |
| In this model pregnant mothers are given IM injections or operation under local anaesthetic to administer drugs to their foetuses in utero, then preterm Caesarean Section delivery under anaesthesia, then their neonates are taken away.  The foetuses have IM injections in utero and/ or an IP injection at delivery. They are the delivered preterm, observed for 5 or 30 minutes, then killed with phenobarbital. | 201 |
| **2.2 MATERNAL DRUG ADMINISTRATION AND POST-DELIVERY FOETAL DRUG ADMINISTRATION / NEONATES KILLED > 1 DAY AFTER DELIVERY (Baboons, rabbits)** | **STUDIES** |
| In this model pregnant mothers have ultrasound, injections, then pre-term Caesarean Section delivery under anaesthesia, then their neonates are taken away.  The neonates then have a variety of procedures to deliver drugs; they may be intubated (in one study without anaesthetic), have a tracheal instillation, have fluids IV, by clysis, or by nasogastric tube. If they are to survive longer they may have a 24 hr glucose infusion. Some might have the following procedures: blood taken, tracheal aspirates taken, IV bolus radioactive palmitate given. They are then killed (pentobarbital, left to suffocate in amniotic sacs) at various time points (at delivery, 6 hours, 1, 2, or 6 days after delivery. | 161, 185 |
| **3. FOETAL DRUG ADMINISTRATION AND FOETUSES KILLED AT DELIVERY (Rabbits)** | **STUDIES** |
| In this model pregnant mothers have operations under anaesthesia for procedures to deliver drugs to foetuses, then hysterotomies or Caesarean Sections 2 -3 days later to deliver preterm foetuses. In only one of these studies was anaesthesia reported for the delivery of preterm foetuses. In one study the mother was stretched on her back, her eyes were covered and traction was applied to quiet her, instead of anaesthesia. In one study the mother was killed and others had their foetuses / new-borns taken away. The fate of most mothers was unreported.  The foetuses had injections in utero and were delivered pre-term 1 - 3 days later. They were either killed upon delivery (by strangulation, severing of the cervical cord followed by thoracotomy, pentobarbital) or left to die of breathing difficulties for up to 6 hours. | 196, 197, 198 |
| **4. OPERATIONS CONDUCTED ON FOETUSES IN UTERO, KILLED PRIOR TO OR AT DELIVERY, OR 1 DAY AFTER (Cows, sheep)** | **STUDIES** |
| In this model pregnant mothers had surgery to conduct procedures on foetuses in utero (anaesthesia reported in all but one study). Some had catheters inserted, some had catheters inserted into their foetuses that then passed through an incision in the mothers’ flanks. In one study mothers had a latex bag left in their uterus. Drugs were administered via mothers to foetuses over several days (7 to 9 days) or fluids taken from foetuses (up to 20 days). Mothers were given antibiotics in one study and blood was taken in another. Mothers were killed prior to delivery in two studies (with pentobarbital). In the other two studies mothers had pre-term Caesarean Section delivery under anaesthesia and their foetuses were taken away.  Neonates had procedures done in utero, including catheterisation and tracheal catheterisation. Only one study reported use of anaesthesia for foetus. Some foetuses then had drugs infused over several days. Some had tracheal fluid withdrawn for up to 20 days. Some had daily injections for 3-5 days. Foetuses were delivered pre-term, most had blood samples taken. In one study foetuses were observed for up to 24 hours for signs of RDS. Foetuses were killed at delivery or 24 hours later (by pentathol and tracheal clamping, pentobarbital to foetus, or pentobarbital to mother), or they died of RDS. | 187, 200, 202, 212 |

**Ventilation models (post-delivery foetal drug administration)**

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| **5. POST-DELIVERY FOETAL DRUG ADMINISTRATION, THEN FOETAL VENTILATION, THEN FOETUSES KILLED (Rabbits)** | **STUDIES** |
| In this model no information is given on the mothers. The rabbit foetuses are delivered preterm, they have a tracheal tube placed (one with anaesthetic one without anaesthetic) and have agents delivered via the tracheal tube. They then have manual ventilation followed by 15 minutes of mechanical ventilation, after which they are killed by plugging the endotracheal tube for 5 minutes and lidocaine. | 206, 208 |
| **6. MATERNAL DRUG ADMINISTRATION AND / OR POST-DELIVERY FOETAL DRUG ADMINISTRATION, THEN FOETAL VENTILATION, THEN FOETUSES KILLED (Sheep, rabbits, monkeys)** | **STUDIES** |
| In this model pregnant mothers are given drugs either IM or IV or both, some for several weeks. Some may also be given progesterone. Then they have pre-term delivery by Caesarean Section under anaesthesia and their foetuses/ new-borns are taken away.  Some foetuses were killed at birth but most killed after procedures. Most foetuses have anaesthesia, but some do not and in one study animals are paralysed and not anaesthetised. All foetuses have an endotracheal tube placed, during which upper airway leaks were reported in one study. Foetuses are then given agents, either by injection or directly into trachea. They then have mechanical ventilation for various amounts of time (ranging from briefly, 15, 30, or 40 minutes, 1 or 3 hours). During ventilation some had pneumothoraces. During ventilation some foetuses were paralysed and some were given pentobarbital to prevent spontaneous respiration. Some studies involved clamping the trachea during or after ventilation. Some foetuses also had catheters inserted and drugs delivered through these. Foetuses in one study had a glucose infusion Dextrose and a chest x-ray. After ventilation foetuses were killed using a variety of methods (including pentobarbital, pentobarbital and tracheal clamping and exsanguination, lidocaine, obstruction of endotracheal tube and lidocaine, endotracheal tubes plugged for 5 minutes). | 177, 165, 166, 167, 168, 170, 171, 169, 179, 182, 195 |

**Ventilation models (foetal drug administration in utero)**

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| **7. MATERNAL DRUG ADMINISTRATION AND/ OR FOETAL DRUG ADMINISTRATION IN UTERO, THEN FOETAL VENTILATION, THEN FOETUSES KILLED (Sheep/ rabbits)** | **STUDIES** |
| In this model pregnant mothers had injections of agents and/ or procedures to deliver agents to foetuses in utero (laparotomy under anaesthesia, intra-amniotic injection or ultrasound-guided foetal injection). Some had additional ultrasounds and progesterone prior to drug administration. They then had pre-term Caesarean Section delivery under anaesthesia, with additional procedures being conducted (to foetuses) at delivery, then their foetuses/ neonates were taken away.  Foetuses were given intra-amniotic or foetal injections in utero. At pre-term delivery they had endotracheal tubes placed either before or after delivery. Anaesthesia and/or sedation for this was reported in only two studies. Some had fluids aspirated and in one study an agent was delivered intratracheally. Foetuses were placed on ventilators, mostly for 40 minutes but in one study for 4 hours. Pneumothoraces or PIE during ventilation were reported in one study. In one study foetuses had the tracheal tube clamped. In one study foetuses were given a hypoxic challenge during ventilation. Some had catheters placed, some had blood taken, some had a glucose infusion, some had albumin delivered via the catheter. Some foetuses were killed at delivery by severing the cervical cord or leaving foetuses to die of breathing difficulties (some took up to 2 hrs to die). Most foetuses were killed after ventilation using pentobarbital, or pentobarbital followed by tracheal clamping and/ or exsanguination. | 176, 158, 183, 186, 188, 208 |
| **8. FOETAL DRUG ADMINISTRATION IN UTERO, THEN FOETAL VENTILATION, KILLED AFTER VENTILATION (Sheep, baboons)** | **STUDIES** |
| In this model pregnant mothers had procedures for ultrasound-guided IM injection of agents to foetuses. Sedation for this procedure was reported in only one study. In one study mothers had the injections to foetuses done twice. Some mothers had additional ultrasound and in one study amniocentesis was performed. The mothers then had preterm Caesarean Section delivery under anaesthesia (although anaesthesia was not reported in two cases. Then their foetuses/ neonates were taken away. In one study mother baboons were monitored after delivery and released to outside cages after 4 weeks.  Foetuses had injections in utero and were then delivered preterm. They had endotracheal tubes placed, usually under anaesthesia but anaesthesia was not reported in two studies. Some had lung fluid withdrawn, some had intra-tracheal instillations and some had the endotracheal tube clamped, some were given surfactant whilst being rotated. Foetuses were then placed on ventilators for 40 or 50 minutes, 1, 2, 3, 4 or 24 hours. During this time some were given agents to prevent spontaneous breathing. Most had catheters placed and were given glucose infusions. In one study where foetuses were kept alive for 24 hours, neonates were given IV inulin, parenteral fluids, antibiotics. In two studies maternal blood was given to foetuses. In most studies blood was taken from foetuses and in three studies albumin was injected. In one study radiolabelled microspheres administered. After ventilation foetuses were killed using a combination of pentobarbital and endotracheal tube clamping and/ or exsanguination. | 195, 204, 206, 207, 209, 210, 211 |
| **9. NO DRUGS, FOETAL VENTILATION, KILLED AFTER VENTILATION (Sheep)** | **STUDIES** |
| In this model pregnant mothers had pre-term Caesarean Section delivery under local anaesthesia and their foetuses were then taken away.  The foetuses had tracheostomy at delivery under local anaesthesia, then suction, then ventilation for 2-5 hours. Catheters were placed. They were then killed after ventilation (manner of death not reported). | 199 |

**Ventilation models (operations conducted on foetuses in utero)**

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| **10.1 OPERATIONS CONDUCTED ON FOETUSES IN UTERO, THEN FOETAL VENTILATION, THEN KILLED (Sheep)** | **STUDIES** |
| Pregnant mothers had hysterotomy under local anaesthesia for procedures to foetuses. Foetal catheters placed that pass from uterus through incision in mother and attached to mothers’ flanks. Drugs delivered to foetus via catheters attached to mothers every 8-12 hours for up to 14 days. They have preterm Caesarean Section delivery under anaesthesia and their foetuses are then taken away.  The foetuses have catheters placed in jugular vein while in utero, then drugs delivered for up to 14 days via catheters. They are delivered preterm, tracheotomised, ventilated for unknown length of time and catheterised. Some are then killed (manner of death unknown) and others are left to die of RDS. | 199 |
| **10.2 OPERATIONS CONDUCTED ON FOETUSES IN UTERO AND AT DELIVERY, THEN FOETAL VENTILATION, THEN KILLED (Sheep)** | **STUDIES** |
| Pregnant mothers had surgery under anaesthesia to perform procedures on foetuses, Foetal catheters placed that pass from uterus through incision in mother and attached to mothers’ flanks. Mothers given antibiotics. Drugs delivered to foetuses via catheters. Mothers then have Caesarean Section delivery under anaesthesia and their foetuses are taken away.  The foetuses had arterial and venous catheters placed in utero without anaesthesia. They then had IV infusions and 5 IV bolus injections administered. At preterm delivery they had anaesthesia for placement of an endotracheal tube and some had foetal lung fluid withdrawn. Some had the endotracheal tube clamped. Foetuses had blood taken and agents administered via the endotracheal tube. Foetuses were then placed on ventilators for 85 minutes or 2 hours. Those ventilated for 2 hours had an artery catheterised and glucose infused. After ventilation foetuses were killed by pentobarbital, or by clamping the ET tube for 5 minutes after pentobarbital. | 203, 205, |