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Paracetamol Treatment for PDA Closure in Preterm Infants

Maintenance of the fetal Patent Ductus Arteriosus (PDA) is critical for diverting circulating blood from the non-breathing lung. Following birth, the closure of a PDA is the normal physiological transition to post-natal life. Persistence of the PDA in preterm infants is associated with comorbidities such as pulmonary hemorrhage, Necrotizing Enterococcus (NEC), Bronchial Pulmonary Dysplasia (BPD), Retinopathy of Prematurity (ROP), death. Management of the preterm PDA ranges from conservative medical management, medical treatment with ibuprofen or indomethacin, or surgical ligation. The timing and type of this intervention is frequently debated. Since these medical and surgical interventions all carry risks to preterm infants, efficacy and safety of various treatment modalities are often balanced against possible side effects.

Complicating these treatment approaches is the variable patency based on gestational age. Approximately 80% of premature infants who are greater than or equal to 29 weeks at birth will achieve spontaneous permanent closure of their PDAs. It seems reasonable to manage these infants conservatively-e.g., allow their PDAs to close, and only intervene if they become hemodynamically significant. For premature infants born at 28 weeks or younger, the rates of spontaneous permanent closure drop to below 40%; and drop to approximately 10% for 24-week preterm infants and below. The PDAs of ELGANs (extremely low gestational newborns < 28 weeks gestation) may therefore be more suitable targets for medical treatment interventions. The current medications FDA-approved for treatment of PDA in preterm infants include intravenous ibuprofen lysine (Neoprofen®) and intravenous indomethacin (Indocin®). As with any medication, there may be side effects, which for these medications may include changes in platelet function, as well as variable degrees of gastrointestinal and renal toxicity. In the search for other medications for PDA closure, enteral formulations have been utilized with variable success, and an observational study published in 2011 by Hammerman et al., identified enterally-administered paracetamol as a possible alternative for PDA closure in preterm infants. / *Continued page 2.*

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Bioethics of Fetal Surgery

Background:

Fetal surgery represents a broad spectrum of techniques that are used to treat birth defects in fetuses in utero. The most common conditions treated with fetal surgery are: neural tube defects, congenital diaphragmatic hernias, congenital cystic adenomatoid malformations, congenital heart diseases, pulmonary sequestrations and sacrococcygeal teratomas.¹ There are several categories of fetal surgery: **1.** Open fetal surgery, a method that involves completely opening the uterus to operate on the fetus, **2.** Fetendo, an approach that uses real time video imagery to guide surgical instruments into the uterus to perform surgery on the fetus, and **3.** Exit procedure, a surgical technique that is used to deliver babies who have airway compression.

The first fetal surgery was performed in 1981 by Dr. Michael Harrison, "the father of fetal surgery", at UCSF Children's Hospital.² He performed a vesicostomy for congenital hydronephrosis. After this first fetal operation, new techniques with less invasive forms have allowed additional defects to be treated.

A milestone in the history of fetal surgery is the MOMS trial. This was a multicenter randomized trial of prenatal versus postnatal repair of myelomeningocele done in 2002. According to this trial, prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at thirty months but was associated with maternal and fetal risks. The success of this trial inspired formation of The North American Fetal Therapy Network (NAFTNet) in 2005 to promote multi-institutional trials on fetal surgery in the United States and Canada.

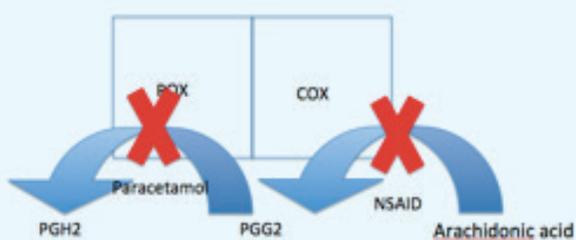
Open Fetal Surgery Technique

Any type of fetal surgery requires a multidisciplinary approach including pediatric surgeons, obstetricians, neonatologists, radiologists and anesthesiologists. Open fetal surgery involves administration of general anesthesia to the mother in which the anesthetic agent crosses the placenta and the fetus receives satisfactory anesthesia. To control and prevent labor, tocolytics are used during and after surgery. The uterus is exposed with an abdominal incision and then it is lifted up. Subsequently, another incision is made in the uterus to expose the fetus to access and perform the surgery. The fetus remains connected to the placenta throughout the procedure. Once the surgery is completed, the fetus is returned to the uterus and the amniotic fluid is replaced. Then, the uterus is sutured and put back in the abdomen. Finally, the abdominal incision is closed. After surgery, the mother and the fetus are kept under observation. The infant is usually delivered³

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Paracetamol is well-tolerated by infants and children for its analgesic effects and may be used post-operatively in NICU settings. It is best known for pain control mediated through the central nervous system. However, the use of paracetamol for PDA closure is a relatively new medication, and there is very limited data for safety and efficacy in this ELGAN patient population. There are currently two proposed mechanisms of action for paracetamol-mediated closure of PDA. Prostaglandin H2 synthetase (PGH2 synthetase) has two components, the cyclooxygenase (COX) component and the peroxidase (POX) component. One theory claims that paracetamol directly inactivates the COX component. The other hypothesis proposes that paracetamol inactivates the POX component, which blocks the transformation of prostaglandin G2 (PGG2) to prostaglandin H2 (PGH2) (Figure 1).

Figure 1. Prostaglandin H2 Synthetase



There are no studies that address the safety and efficacy of paracetamol use in preterm infants. It is known that high serum paracetamol levels may cause a direct hepatotoxic insult from its metabolite. Paracetamol is metabolized in the body via UDP-glucuronosyltransferase 1A6 enzyme into paracetamol-glucuronide (APAP-G) and paracetamol-sulphates (APAP-S), 1-4% is excreted unchanged through the kidneys, and 8-10% is further oxidized to 3-hydroxyl paracetamol and N-acetyl-p-benzo-quinone-imine (NAPQI) via liver cytochrome P450 2E1. It is this NAPQI metabolite that has a direct toxic effect on hepatocytes (seen in acetaminophen overdose). When the serum level of paracetamol is within range, endogenous glutathione further conjugates NAPQI into cysteine and mercaptic acid into non-toxic forms that are excreted. It has been proposed that when increasing serum paracetamol levels overwhelm endogenous glutathione, NAPQI accumulates and acts directly on hepatocytes, and manifests as liver injury with elevated aspartate transaminase (AST) and alanine transaminase (ALT) levels.

Though there are studies that are currently in print claiming success of PDA closure using paracetamol, these studies are mainly observational, with small patient numbers, using different dosages (ranging from oral 7.5 -15mg/kg/dose q6h) with variable treatment durations (ranging from 3-7days). The subjects were more mature preterm infants, who were born with birth weights above 1 kg. One of the major criticisms for these studies is that the background spontaneous closure rates were not taken into consideration. Therefore it is unknown from these studies whether paracetamol is truly effective in facilitating closure of PDA.

Currently the effective serum level for PDA closure in preterm infants with paracetamol has yet to be established. In addition, potential hepatotoxicity effects have not been investigated in preterm infants. To address the issues of serum steady state elimination, and toxicity of paracetamol in preterm infants, Ganzewinkel et al investigated the pharmacokinetics of paracetamol (IV) when given for pain control. Fifteen preterm infants born less than 32 weeks gestational age were given five repeated doses (7.5mg/kg/dose) of IV paracetamol for pain control. They found that with repeated IV doses, the endogenous

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glutathione level did not decrease over time, and the AST/ALT levels were not significantly elevated above 50 U/l. They also found that serum paracetamol reached steady state around 31 hours after the first dose, and the metabolism changed with gestational age. Ganzewinkel also concluded that clearance of paracetamol increased with post-menstrual age as well as with increasing birth weight. Though these numbers are promising in terms of the safety of IV paracetamol, it is still unknown if the more available and less expensive oral form of paracetamol shares the same bioavailability and pharmacokinetics as the IV form; and, whether this is efficacious in PDA closure in ELGANs.

Paracetamol is a drug used by neonatologists for pain control in preterm infants; however, the proposed application of oral paracetamol for PDA closure is relatively new. With limited data on safety and efficacy of paracetamol (particularly enterally-administered) use in ELGANs, and in particular when used for treatment of PDA, it would seem that caution should be exercised. Pharmacokinetics following enteral administration, comparisons to established safety and efficacy profiles of IV ibuprofen and IV indomethacin, particularly in ELGANs, would seem to be prudent before oral paracetamol achieves another medical treatment for PDA closure of ELGANs.

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by planned caesarian section at approximately 36 weeks gestation, unless premature labor or other complications occur before that time.³

Bioethical aspects of fetal surgery

One ethical consideration for the clinician with fetal surgery is to assess the benefits and risks of the procedure to both pregnant woman and the fetus. The clinician should respect the autonomy of the pregnant woman and obtain informed consent for the procedure^{4,5} The consent should be taken by a physician competent to explain the intervention and its alternatives with its risks and benefits. The consent should be non-directive and should avoid therapeutic misconception.

The mother, the fetus, the physicians and on a larger scale the society may benefit from fetal surgery. Fetal surgery might mitigate the anxiety for the mother caused by awaiting the birth of a fetus with known medical problems. Fetal surgery can also improve the condition of the fetus or it can possibly prevent its death. The physicians may be relieved to act upon a known fetal threatening diagnosis. There could also be a decrease in the burden of sick or disabled people to the society.

All these benefits have to be balanced with the risks of the procedure. The overall perinatal mortality after open surgery has been estimated to be approximately 6%. The safety depends on the specific procedure, the gestational age and the condition of the fetus. The costs of the procedure have to be taken into account as well.

The specific risks for the pregnant woman in open fetal surgery include: uterine rupture, additional C-sections, premature labor and delivery, exposure to multiple drugs and prolonged hospitalization. The risks for the fetus involve premature delivery, exposure to anesthesia, failure of surgery and fetal demise⁶. There is a risk of incremental harm from intervention, possibility of iatrogenic versus natural disability, a child with a severe disability versus a child with milder disabilities or no child.

In summary, the trade-offs for the pregnant woman who has a fetal candidate for surgery include: her risks versus her benefits, her fetus's risks versus her fetus's benefits, her risks versus her fetus's benefits and her fetus's risks versus her benefits.

The physicians have obligations to the fetus as well as to the expecting mother. An ethical dilemma exists when the desires of the mother oppose needs of her fetus. This dilemma is resolved by taking into consideration the viability of the fetus. Viability is defined as the ability of the fetus to exist ex utero with or without technological support. If the fetus

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is viable, the needs of the fetus may take precedence over the wishes of the pregnant woman. If the fetus is not viable, the pregnant woman's decision should be respected.

The pregnant woman should be allowed the freedom to decide upon alternative courses of therapy based on her values and beliefs¹⁰. However, society expects that pregnant women to be altruistic. The ideas of maternal altruism do not fit into an autonomy-based ethic system.¹¹

Another potential conflict can arise when the maternal and paternal desires are not the same. US federal regulations are distinctive in the international context in continuing to require the consent of the father for fetal research, including maternal fetal surgery. This allows undue influence or even control over the pregnant woman's autonomy by someone who bears none of the medical risks. The ACOG Committee Opinion is as follows: "Although it may be appropriate and helpful for the father to be involved in these decisions and have complete access to information, to assign him any authority to assent or dissent would unjustifiably erode the autonomous decision-making capacity of the pregnant woman."

Progress in medical practice depends on innovation; however surgery on the fetus is always surgery on the pregnant woman as well. Ethical obligations to both must be taken into account in the design and conduct of research on maternal-fetal surgery.

In conclusion, fetal surgery is still not yet standard of care and can be justified when:

- (1) There is reasonable certainty that the fetus will suffer irrevocable and substantial harm without the intervention;
- (2) The intervention has been shown to be effective and it has a realistic chance of saving the life of the fetus or preventing serious and irreversible disease and disability.
- (3) The risk to the health and well-being of the pregnant woman is negligible;
- (4) The pregnant woman can give appropriate informed consent to the intervention.

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14th Annual Hudson Valley Regional Perinatal Public Health Conference

The 14th annual Hudson Valley Regional Perinatal Public Health Conference, *"Hot Topics in Perinatal Health: Social Media, Donor Milk, Paternal Impact, and Reproductive Environmental Health"* was held November 4th, 2015 at the DoubleTree in Tarrytown, NY. The conference was hosted by the Regional Perinatal Center at Maria Fareri Children's Hospital(MFCH)/Westchester Medical Center Health Network, the Lower Hudson Valley Perinatal Network (LHVPN) and Maternal Infant Services Network with major sponsorship from Children's Health & Research Foundation and March of Dimes. Over 120 health, medical and human services professionals from the seven counties of the Lower Hudson Valley attended.

Dr. Michael Gewitz, William Russell McCurdy Physician-in Chief; Chief, Pediatric Cardiology, Maria Fareri Children's Hospital, gave the welcoming remarks commenting on the importance of public health conferences in shaping healthcare and reaching communities.

The first speaker of the day was Dr. Andrew Elimian, FACOG, Professor, OB/GYN, NY Medical College; Director, Maternal Fetal Medicine, WMC, who presented *"Premature Birth: Can it be Prevented?"* The talk focused on causes, pathways, and trends of preterm birth. Dr. Elimian addressed the global impact of prematurity and the numerous international prevention efforts.

The morning keynote speaker was Dr. Marya G. Zlatnik, MMS, Associate Director, Maternal Fetal Health & the Environment, UCSF-Western States Pediatric Environmental Health Specialty Unit, presenting *"Environmental Contaminants & Reproductive Health: What Should We Tell Women?"* Dr. Zlatnik addressed the increase in chemicals in our everyday lives, their potentially harmful role in reproductive health, and how to counsel pregnant women regarding these environmental hazards. She concluded her talk with 10 easy to follow steps on avoiding contaminants, such as which foods to choose based on likely levels of pesticide residuals, organic vs. non-organic.

The late morning keynote speaker, Dr. Nathaniel DeNicola, MSHP, FACOG, Faculty in Obstetrics & Gynecology at University of Pennsylvania; Senior Fellow, Penn Social Media & Health Innovation Lab, presented *"The Doctor Will Tweet You Now: Professional Use of Digital & Social Media in Public Health Advocacy"*. Dr. DeNicola discussed the role of social media in healthcare, including online data being used

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to predict heart disease, how research and collaboration can be facilitated through social media, and the necessity of responsible social media use.

The afternoon keynote presentation was delivered by Jermaine Bond, PHD, Program Director, Boys & Men of Color, National Collaborative for Health Equity. Dr. Bond presented *"The Paternal Factor: Evidence, Strategies, & Innovations,"* a talk focused on the important role of paternal involvement in pregnancy. The session touched on historical and contemporary aspects of fatherlessness, related socioeconomic factors, and recommendations to better involve fathers, as well as research on paternal impact.

Dr. Boriana Parvez, Medical Director, Donor Preterm Human Milk Bank, Westchester Medical Center Health Network, presented *"Benefits of Donor Milk in the NICU"*, a talk focused on the importance of breastfeeding and how to increase rates. She described how donor milk banks help improve short and long term outcomes of both infants and mothers. Initial results at MFCH showed significant improvements in breastfeeding as a result of donor milk availability.

Dr. Edmund F. La Gamma, FAAP, Chief, Division of Newborn Medicine, Professor of Pediatrics, Biochemistry and Molecular Biology, NY Medical College; Chief, Regional Neonatal Center, Maria Fareri Children's Hospital at WMC presented *"State of the Region's Perinatal Health"*. He spoke on national trends in births, prematurity and related ethical issues, breastfeeding, and drug related discharges. Dr. La Gamma touched on the RPC at WMC and its role as a referral center for the region, as well as various NYS DOH public health initiatives. Dr. La Gamma also spoke briefly about the emerging problem of high rates of survival just below the upper limit of a legal termination of pregnancy at 24 weeks gestation and how this represents a paradox for clinicians in the delivery room regarding whether a child's right to a trial of therapy as valued by the provider can be superseded by a parental right to decline care. The option of delivery room hospice was discussed as a compromise position in extraordinary circumstances where no clear path to reconciliation materializes.

Closing remarks were made by Cheryl Hunter-Grant, LMSW, CLC, Executive Director, LHVPN. Her take-home message was one of collaboration on all fronts in an effort to provide access to health care and promote health equity toward improving perinatal health outcomes throughout our region.

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