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Sitting Down with Dr. Shinjiro Hirose: The Ins and Outs of Fetal Surgery

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Imagine you are in a crowded operating room. It teems with neonatologists, radiologists, anesthesiologists, obstetricians, neurosurgeons and ancillary staff. But the two most important people in the room are the patients lying before you. The fascinating thing is your patient has not even been born yet. This is the typical day for a fetal surgeon like Dr. Shinjiro Hirose, an Assistant Professor of Surgery at the University of California at San Francisco Division of Pediatric Surgery and Fetal Treatment Center. The editors of *Quill & Scope* sat down with Dr. Hirose to discuss his unusual specialty.

QS: How did you end up in fetal surgery?

Dr. Hirose: That's a good question. It started actually with my interest in pediatric surgery. I will back up to give you an idea of where it all starts. After I graduated from New York Med, I went to UC Davis for general surgery. After doing three years there, I planned to spend some time in a lab, which you generally have to do in general surgery to match into something like pediatric surgery or transplant surgery – one of the more competitive specialties. I started looking around for labs to do some pediatric surgery research. There are several across the country, famous for having research fellows. Both of my brothers were at UCSF at the time. My older brother had completed his general surgery residency and transplant fellowship at UCSF, and was in his last year of his fellowship at the time. My younger brother was actually a general surgery resident there as well. So I talked to my older brother, who has been a great mentor to me, and he said, "Why don't you just come to UCSF, they have a great tradition and lab, etc. So I asked Dr. Mike Harrison [Division Chief in Pediatric Surgery at the Children's Hospital at UCSF, established first Fetal Treatment Center in the U.S.], "Hey, do you have space in the lab?" And he said, "Sure, come on down." So that was basically it. I set up to work in the lab at UCSF for two or three years, it turned out to be three. I did fetal surgery research for three years, and general pediatric surgery research as well – that's clinical. I did half clinical and half basic science research. That's how it all started. It's hard to match the "fun-factor", the "science -factor" and the "cutting-edge factor" of fetal intervention and put it all together, and then be able to intervene on patients. It's really a fantastic field.

QS: How large is the usual team for a fetal surgery?

Dr. H: It depends on the case, but as you can imagine, there's a lot of people. Fetal surgery is really a team sport. It's not just the surgeons, it's really a whole cadre of people. To start off, in terms of all the discussions, we have a weekly multi-disciplinary meeting that includes a whole gamut of people: from the fetal surgeons, to the perinatologists, the obstetrics-gynecologist, the neonatologists, the pediatricians, the radiologists who do mostly ultrasounds for us, the neuroradiologists, the pediatric cardiologists, social work, nursing, and of course all the students and residents. So it's a big meeting. We also have anesthesiologists come to the meeting too. We have anesthesiologists that specialize in fetal anesthesia because the mom's anesthesia is critical to keep the uterus relaxed. There's a big anesthesia team. In the operating room for each case, there is usually a minimum of two attendings, two surgeons, an obstetrician, an ultrasonographer, a radiologist who has scrubbed, two to three nurses – it starts to get to be a pretty big team. That's generally the minimum.

QS: What's the frequency which you get together with this big team and perform fetal procedures?

Dr. H: It depends on the diagnosis. Right now the most common thing we do is surgery for problems with *monochorionic twinning*, and most commonly *twin-twin transfusion syndrome* where we use a laser to endoscopically divide the shared blood supply between the two twins. I can't cite the exact incidence because the number keeps on going up. I would think that we do an average of three or four a week, but it ebbs and flows.

QS: With so many members on the surgical team, do you see many conflicts, where some push for surgery and others are opposed to it?

Dr. H: Sometimes. It's actually not that common, because in general we hash it out until we get consensus. If there's true disagreement there has to be a reason, and opinions don't count. If someone has a strong feeling, it usually has to be based on data. The truth is, there isn't a lot of data, so then it comes down to a lot of conjecture. The bottom line is, sometimes it comes down to the tie breaker, which is usually the fetal surgeon. That's what it boils down to, because someone's shouldering the decision-making risk, and in general it's the surgeon.

QS: What are your "bread and butter" cases, if you have "bread and butter" cases for fetal surgery?

Dr. H: There aren't really bread and butter ones, I would say the twin cases are probably the most bread and butter at this point. But they are still so specialized, really each one is sort of a big deal.

QS: Would you say fetal surgery is still kind of experimental?

Dr. H: A lot of it is, yes. The truth is there's never been a prospective randomized trial to show that surgery for appendicitis is better than antibiotics. Actually, for certain situations like a missed appendicitis where there's an abscess we often won't operate and we'll treat the patient with antibiotics, cool them off and do what's called an interval appendectomy two months later. There's also never a prospective randomized trial to say that laparoscopic cholecystectomy is better than open cholecystectomy. In fact, if there was, there probably would've been a halt in the trial because initially the rate of common bile duct injury was either 10 or 100 times higher in laparoscopic cholecystectomy than open cholecystectomy. It was much higher. The rate subsequently came down with the learning curve. A lot of the stuff we do in surgery becomes accepted because it seems intuitively obvious that you should do it that way. The truth is, fetal surgery will probably never be that way. The reason is because it's not just the charged issue of operating on an unborn baby, but mom's involved and you risk having a 200% mortality for one case. In general I think most procedures will be considered experimental, although [in the case of] the twin interventions and interventions for babies with non-immune hydrops or inter-utero heart failure, I think there are pretty clear indications for fetal surgery.

QS: So fetal surgery has the potential for 200% casualty rate; do you see the health of the mother as a kind of a limitation?

Dr. H: Absolutely. First of all, if the mom has any significant medical problems, you can't really offer fetal operations. If mom has significant issues with her uterus, for example if she

has a large fibroid, we tend not to offer fetal operations. Mom is really the most important person actually. The fetus is kind of secondary. The mom has to be the most important person.

QS: Do you consider mom to be your patient?

Dr. H: Absolutely, they're both your patient. This gets touchy because some people feel that the fetus has rights that are being ignored, and who's standing up for the fetal rights? Who says that a fetus wants the operation? To step back, there's a phrase coined about fetal surgery in general. My boss, my mentor Mike Harrison is an ethicogenic person. He generates ethical dilemmas. Fetal surgery is a big ethical dilemma. First of all, you can talk ad nauseum about the rights of the fetus. You'll never answer that question, because which fetus is going to tell you what they want? And there's no real answer for that.

QS: Just listening to what you're saying, it sounds like your field is self limited because you have to take into account the health status of the mother for the duration of surgery. Do you find it limiting or exciting that you have these kinds of constraints other surgical fields don't have?

Dr. H: I don't find it specifically exciting but it's just one of the things you have to deal with in fetal surgery. I guess I didn't really pay much attention to limitations other than that you have got to take mom's health into consideration. She is really the person that you must minimize risk for because again, she is getting no medical benefit at all. We liken it to a living donor transplantation, where the donor really is getting no medical benefit. They're having a major operation for no medical benefit. And so you really have to be very careful in how you counsel those patients.

QS: You talked about the line, right now you're establishing how far you can go in a fetal operation. Can you share an example of the extent to which you will go?

Dr. H: Well it's interesting - the philosophy, especially for fetal surgery, is first to treat defects in fetuses that were life threatening; things that the baby is going to die from. So then really the only way to go was up. The next thing was to treat defects for which something we do might help. Because there are some things that you might find in-utero that no surgical intervention is going to help. The last thing is really that you have to minimize risk to mom. Minimizing risk to mom probably doesn't change much. The most invasive thing we do is open fetal surgery where the mom has general anesthesia. We do maternal laparotomy, expose the uterus to maternal hysterectomy, expose the fetus, operate on the fetus and then close everything back up. That's probably the most invasive thing we do. I'm not saying it's without risks—there's definitely risk to mom. There is risk from the standard things like a scar, infection, bleeding, risk of blood transfusion. Uterine issues are definitely a big problem because the way uterine incisions are made really has to do more with access to the fetus and avoiding entry into the placenta versus doing the standard lower transverse C-section incisions on the uterus to allow the woman to have vaginal birth after C-section, or what's called a V-back. And often we make an incision on the uterus that's more like a classical hysterotomy, which results in the woman's probably having C-sections for any future pregnancies. Especially in an open fetal surgical case, you have to make sure that the woman understands that and understands those implications. And especially if it's a young woman who can potentially have another baby at another time and one of the options is always termination, at least in 2008 in the United States. Especially for someone who

might have a terrible defect in the fetus with a really bad prognosis and young parents, they may well consider termination of their pregnancy and try again. The truth is that most of the patients that come to us actually want some kind of fetal intervention and have already thought about termination, and don't want to do it. That's another sort of ethnogenic issue with fetal surgery.

QS: What is the time window that fetuses are presented for surgery? Do they have to be a certain month of gestation?

Dr. H: In general, we operate in the 2nd trimester. And generally for most life-threatening abnormalities we operate on a pre-viable fetus, so before 24 weeks. There are some limitations specifically, say, for example, twin-twin transfusion syndrome where we use a laser. We have to do it before the baby's eyes are open which is generally before 26 weeks. If you operate on a baby that has hydrops, say, for example, because of a mass, a chest mass or another very vascular tumor that causes high-output heart failure, you have to temper what you do in terms of whether or not it'd be better for the mom or the fetus to be done at this time. Generally hydrops is an urgent situation but if the baby's viable and older than 24 weeks, then you can argue that you might want to just deliver the baby and take care of the mass post-natally and deal with the complications of prematurity. 24 weeks is pretty early so it's less of a debate, but you know for example if the baby is 27 or 28 weeks you could argue that it's better to deliver and do post-natal therapy instead of doing some kind of in-utero therapy but that's on a case by case basis.

QS: Have you looked at surgical interventions say, 5 years ago, compared to a control in which it hasn't been done and generally how the prognosis is in terms of fetal surgery as compared to before?

Dr. H: Well no, it depends on what you're doing it for. And the short answer is yes. But it depends on what you're doing the intervention for. So for example, if you take a baby that has a mass in the chest that develops hydrops we know from natural history studies that those babies have a near 100% mortality without intervention. And you look at our data and the data from really the one other institution that has published it, the Children's Hospital in Philadelphia, if you do fetal surgery on a baby that has hydrops, you change the mortality rate to about 50%. So, you know it's a big difference. So that kind of data makes it very clear to us if there is a clear indication for surgery or for delivery if the baby is post-viable. There have been other studies that we've done, for example prospective randomized trials for balloon occlusion of the trachea for congenital diaphragmatic hernia. And we did a prospective randomized trial and found no difference in the treatment and control arms for various reasons. That's actually a long discussion but we've abandoned that particular technique for treatment of diaphragmatic hernia. We have another trial going on right now for a new balloon device during temporary tracheal occlusion to see if that helps those babies. But you know all these things again are under the auspices of research protocols.

QS: When you were training or when you want to practice a procedure, do you use a model animal?

Dr. H: Yeah, absolutely. We use all sorts of animal models. We often start with rodents, mice and rats. We do rabbit experiments, they're great because they have litters and not just one baby. So you can do multiple procedures on those fetuses and see how things turn out. The

mouse model is great because you can get a lot of antibodies and do other histological work on them. For large animals, sheep are great because they tend not to have premature labor, their pregnancies are very durable and they tolerate fetal manipulation and go to term. Really, and we haven't done this in a long time, the most experimental things that we do closest to humans now are non-human primate experiments.

QS: Are there procedures or techniques for which you would not do a trial, for example hydrops, where the mortality rate is so high?

Dr. H: We probably won't do a prospective randomized trial in that. That's probably as good data as we're going to get. It's pretty compelling because the difference is big. In terms of medicine, in terms of finding out differences, it's really a slippery slope. Sometimes prospective randomized trials are not the way to go. There will never be one for appendectomy. That's just part of what we do. For fetal masses with hydrops it's fairly clear that doing something for them can potentially save the life of a moribund fetus. I don't think much study necessarily needs to be done for that. If you try a new technique, maybe, some kind of minimally invasive technique such as sclerotherapy or laser therapy then you might want to try to develop an animal model to try a different therapy. In general, open fetal resection is well indicated in that situation.

QS: How do insurance companies react to the service?

Dr. H: That's a good question, and I wish I had a hard and fast answer for that. A lot of times we don't get paid, in terms of surgeon's fees. The hospital tends to get paid their facility fees, so they don't lose money on that. The hospital's happy to have us do the operations, but sometimes we don't get paid and sometimes we do. It depends on the insurance company. For most clinical trials we don't generate a surgeon's fee.

QS: Is there a demographic particularly at risk?

Dr. H: I wouldn't say that there is a demographic particularly risk. There seems to be a preponderance of older couples doing in vitro fertilizations that have problems with their pregnancies. There's an increase for instance in monochorionic twinning in this country, as opposed to in-vitro dichorionic or multichorionic pregnancies with multiple placentae. No one really knows why the trend is going up, but it sure seems to be.

QS: You said that it's usually the mother who is very eager to go for surgery. Comparing different populations do you see any difference among women who are more receptive to having surgery, or are all women equally for it?

Dr. H: I wouldn't say that there's any particular demographic that's more interested in fetal operations, but I will say that it's pretty intuitive that the older women who have had many in-vitro attempts at fertilization, and have this one pregnancy, they're very interested in having everything go right for the baby. Often they want everything done. But in terms of receptiveness to fetal operations, it's pretty even across the board. That was one of things we were worried about when we first started doing clinical trials. We weren't sure mothers would accept coming to the fetal treatment center and us saying, "This is what we can do in terms of fetal interventions, but we don't know if it's the right thing. So we're going to flip a coin and see what we're going to do with you." That's a hard thing to say to somebody, and it's a hard thing for a

patient to accept. We found that there is a remarkably high acceptance rate. For that trial, we had 25 patients that met criteria and 24 were willing to be randomized. Those are pretty good numbers.

It's funny because you know they're coming to the fetal treatment center because they want some kind of fetal intervention. It's a little odd to look them in the eye and say, "I don't know. We can do this, but I can't just do it, we have to see if you will be randomized to treatment. Are you willing to be randomized to the non-treatment arm?"

QS: Are there any that just want to go forward with the surgery?

Dr. H: Yeah. If they're not willing to be randomized they can't be in the study. That's why for some studies, they don't work. If those people who really want surgery have a back door, or another place they can go to get their intervention, then they would do that. Then you'd have no one randomizing to the control arm, the non-treatment arm. So for these trials they either have to be multi-center to involve all the centers that do the procedure, or ones aren't involved in the trial have to be willing to buy into the trial and not do these procedures until we get the results of the trial. That was one of the problems with the US twin-twin transfusion trial: there was a center that didn't stop doing these, so they were a back door for these patients to go to.

QS: For some of these twin procedures, do you have to choose one twin over another?

Dr. H: Sometimes. It's pretty straight-forward, because generally one twin is sicker than the other. In twin-twin transfusion with laser therapy, we're trying not to pick a twin, we're just trying to divide the blood vessels. There are procedures we do where we selectively reduce, or basically kill, one of the twins. It's usually one that has a life-threatening birth defect. Their spontaneous demise puts the normal twin at risk. Instead of it being an uncontrolled demise, we sometimes perform radio-frequency ablation, using a radio-frequency probe to ablate that abnormal twin.

QS: We talked about the perspective of the families. Do you see your patients down the road, in 10, 15, 20 years?

Dr. H: That's a good question. In general, for fetal interventions, they're not that old yet. We have a lack of data in specific cases where we want a neurological outcome. It's one of the things that I'm interested in right now. We're actually in the beginnings of that, so we're doing survey data where we're calling patients and trying to find out how they're doing. We need to get funding so we can bring them back and do formal neurologic testing of the fetuses or the babies that as fetuses underwent different therapies. And that's actually kind of missing in most of pediatric surgery. For example, for most of the neonatal operations we do there isn't a lot of long-term data. Some of those things we've been doing as a field for 20, 30 years so we should have that data, but it's hard to keep track of those patients for 30 years. In particular, for certain congenital abnormalities at UCSF we've started some long-term follow up clinics where we bring kids back, school age, teenagers, and see how they're doing. Not from a clinical standpoint but quality of life surveys to see how they're doing. The focus in pediatric surgery, and which will be in fetal surgery, is not just about survival anymore, it's about quality of life. We know that with a lot of these diseases we can get a surviving patient, but really how good is their life? None of us know those the answers yet, but we need to gather that data.

QS: What is the best way to start gathering that data?

Dr. H: I think bringing the patients back, and seeing them on a regular basis and keeping track of them, if they move away, to know where they are. It's mainly seeing them on a regular basis, maybe just yearly. If you can see your patients yearly, it's not that many patient visits and you can gather a lot of information.

QS: How does the technical aspect of fetal surgery fit in with your mechanical engineering background and interests?

Dr. H: UCSF has a culture of innovation, as well as a place that lets you foster things like fetal surgery. On top of it, we have a clinical innovations group where we brainstorm ideas and create new gadgets for surgical use. For example, one of the things we're working on is *magnets in medicine*. We are currently conducting a trial where we plant magnets in kids' sternums and we have them wear an external brace to correct *pectus excavatum*, which is a chest wall defect where the chest is caved in. For devices such as this we collaborate more with the engineers. There are a lot of engineering issues with that.

In terms of fetal surgery, there are definitely things we do that could be helped by better devices. It's sort of like a pie in the sky, but we'd like to be able to start making more devices to help us do what we do.

QS: What kind of technology is on the top of your wish list?

Dr. H: The top of my wish list is basically something that lets us perform minimally invasively without having to hold the camera or the light source. The dream is to be able to take a little robot, insert it into a port and have it be your camera and light source. It'll move where you want it to move, either by voice or eye command. That'd be great. It's silly in 2008 that we have some big stick that someone has to hold with multiple cables coming off. It's really sort of ridiculous, especially when you have a little ear piece from your phone that you can talk into.

Dr. Shinjiro Hirose is an Assistant Professor of Surgery at the UCSF Division of Pediatric Surgery and Fetal Treatment Center. Dr. Hirose completed his undergraduate education in 1990 at the Massachusetts Institute of Technology in Cambridge, Massachusetts where he received a BS in Mechanical Engineering. Before enrolling in medical school, he performed robotics research in telerobotics at the SECOM Intelligent Systems laboratory and at the Charles Stark Draper Laboratories.

After realizing that his true interests were in medicine, Dr. Hirose then went on to obtain his medical degree from the New York Medical College in Valhalla, New York and matched in surgery at the UC Davis Medical Center where he completed three years of clinical training. Dr. Hirose then spent three years in the UCSF Fetal Treatment Center as a post-doctoral fellow investigating neural regeneration after spinal cord injury and its implications in fetal surgery for myelomeningocele.

After his post-doctoral fellowship, Dr. Hirose remained on and finished his clinical training at UCSF. After his general surgery residency, Dr. Hirose completed his specialty training in Pediatric Surgery at the Morgan Stanley Children's Hospital of New York at Columbia University in New York City. Dr. Hirose's interests and specialties include minimally invasive surgery, fetal and neonatal surgery, hepatobiliary surgery, bariatric surgery, robotics, and surgical education. His research interests include fetal surgery for disorders of twin gestations, congenital diaphragmatic hernia, myelomeningocele, and gastroschisis.