

Collaborative on Health and the Environment (CHE)
Environmental Contaminants and Fertility/Early Pregnancy Compromise Working Group
Implantation/Miscarriage and Environmental Chemicals
Teleconference # 8 Thursday, Dec 8, 2005 9:00-10:00 am Pacific (41 callers)

ALISON CARLSON: This is Alison Carlson, facilitator of CHE's Work Group on Environmental Contaminants and Fertility/Early Pregnancy Compromise. Welcome to our 9th teleconference. I will cover a couple of logistical details, then turn the call over to our moderator, Steve Heilig.

This call is being recorded, so we can post an audio file and transcript behind password on the CHE Fertility member Web page, for those who have to miss the call. We also hope we might be able to share the transcript in strategic ways, if that's appropriate, to encourage other health professionals more generally in considering environmental factors with regard to assessment, clinical research and practice, etc.

With that in mind, I want to note the participant list I circulated with your call reminder. We have a number of guests on today's call who are not technically members of CHE Fertility, but were at the Vallombrosa Workshop, or are from the Reproduction and Environment Special Interest Group that's forming inside the American Society for Reproductive Medicine. I want to welcome Dr. Lynn Westphal from Stanford; Gloria Davis from the Ochsner Foundation Clinic; Rebecca Sokol from Keck School of Medicine; Kurt Barnhart and his colleague, Alka Shaunik from U Penn; John Holden; Antonia Gilligan from Alpha Environmental; Salim Daya from McMaster.

We also have guests from the California Department of Health Services: Janice Prudhomme, a public health medical officer with the Hazard Evaluation System and Information Service - and Julia Quint, a research scientist who is chief of that office. And we have Vivian Lewis, professor of Ob-Gyn and Director of REI at the University of Rochester. And finally Barbara Siebert, from Planned Parenthood Continuing Medical Education and Women's Health Nurse Practitioners Program.

A mark-your-calendar's announcement: The dates for the UCSF-CHE Summit on Environmental Challenges to Reproductive Health and Fertility are now confirmed and public. January 28th through 30th 2007 at UCSF's Mission Bay Campus in San Francisco. We'll be getting program registration and other information out later this spring and over the summer. In the meantime, you can find basic information on the Web page of UCSF's Ob-Gyn Department, under "Research Programs/Centers." If you can put a Save The Date on your web or organizational calendars, we'd appreciate that. To get a blurb with the details for your calendars, just email me.

I'd like to turn the call over to our moderator Steve Heilig, Director of Public Health and Education at the San Francisco Medical Society, and the Collaborative on Health and the Environment. Steve?

STEVE HEILIG: Today's agenda includes three speakers from infertility specialist fields who have experience developing and using environmental questionnaires as a part of clinical research. We have asked them to take 6-7 minutes each to describe their studies and envi history gathering [i.e. how they went about designing/vetting their questionnaires; what they think the critical elements and issues of envi history-taking are in repro med settings or in general; what has worked, what hasn't – how their efforts are shaping up. We hope to learn what their challenges have been, and what important lessons they would advise colleagues about who may be interested in paying attention to environmental factors in practice and/or research].

We also invited a Utah-based obstetrician, Dr Kirtly Parker Jones, [who sees a patient population that includes a number of “downwinders” from past nuclear testing and several superfund sites upwind of Salt Lake City. We were eager to specifically include comments from a medical professional dealing primarily with couples or patients further upstream in reproductive journeys than our repro med specialists typically do, with couples just beginning to contemplate or begin family-building, or patients thinking about fertility preservation... To get perspective on whether or how Dr Jones and her “upstream” colleagues address envi repro health realities; and her sense of whether and how they should or should not go beyond “boilerplate” generalizations of eating well, getting sleep, not drinking alcohol, etc to incorporate envi health, histories and recommendations into their practices.]

Unfortunately Dr Jones is unable to join us today. We hope to have her on another time. [We plan instead to call on other reproductive health practitioners we are pleased to have on this call who can step in and speak also to this upstream perspective during our discussion.]

Just by way of background, as well: Alison has previously mentioned the Vallombrosa Statement ... For those of you have not been part of this process to date, that is a result of a remarkable [CHE Fertility] meeting at Stanford University, at the conference center called Vallombrosa [in Menlo Park, CA]. You can find the Statement on CHE’s home Web page, at www.healthandenvironment.org, in the "What’s New?" column on the left side. It takes you to the page for the fertility/pregnancy compromise working group. [The Statement covers the science behind debates about practitioner recommendations in regard to envi repro health.]

We're going to begin presentations with **Dr. Ted Schettler**, who is a physician and Science Director of the Science & Environmental Health Network. He’s spent a lot of time developing medical and professional training in environmental health. (Anyone who has worked in medical schools and other training environments, knows it can be very difficult to inject new ideas into standard curricula.) We're going to have Ted set some context [for our speakers – or for what his take on this topic has been].

TED SCHESSLER: Historically, there has been a tendency to believe that people are generally “protected” from the surrounding environment, Except for large exposures or major perturbations that could overwhelm what some people thought of as defense mechanisms. For example, even though it has been known since biblical times that alcohol consumption during pregnancy can damage the developing child, until fairly recently, impacts were considered limited to really quite large exposures.

25 or 30 years ago, little routine attention was paid at all to environmental factors that could influence fertility or pregnancy outcome. At that time, inquiries were largely limited to alcohol consumption, tobacco use, and a few pharmaceuticals. Though even for those, there was little consensus about their importance, and considerable variability in practice patterns. In fact, some obstetricians thought that small amounts of alcohol might actually be beneficial. I've heard anecdotally that some continue to believe that, today.

To set a context for today’s discussion, I'd like to review a few of the important events of the past several decades that began to draw increasing attention to the role of environmental factors in fertility and pregnancy outcomes. Perhaps among the most-dramatic, the tragedy of Minamata Bay in Japan unfolded in the 1950s. There, pregnant women who consumed fish that was highly contaminated with methylmercury gave birth to children with severe neurological damage – including mental retardation, seizures and cerebral palsy and so on. It became apparent that the developing fetus was much more susceptible to the neurotoxic effects of methylmercury than adults.

There were similar episodes in Iraq in the 1970s, when pregnant women ate bread made from grain that had been treated with methylmercury as a fungicide and intended for planting rather than direct consumption. In the 1960s, thalidomide was used in about 1% of pregnant women in Europe and Australia, to treat morning sickness. It soon became apparent that thalidomide caused a dramatic increase in the incidence of severe limb deformities, when the exposure occurred during the 5th to 8th weeks of pregnancy.

And the use of diethylstilbestrol [DES] during pregnancy in the 1950s, '60s and early '70s sharply increased the risk of deformities of the reproductive track and later reproductive-tract malignancies in female offspring. There's also evidence of reduced fertility and reproductive abnormalities in males.

It also became apparent that chemical exposures could impair male fertility. Shell and Dow chemical companies had begun to produce a soil fumigant called dibromochloropropane (DBCT). It was used to protect a variety of fruit crops from soil nematodes. Early tests showed that DBCT damaged the testes in three different animal species. But the manufacturers did not report that information, nor act on it. As a result, in the 1970s it became apparent that many men occupationally exposed to DBCT were sterile, or had reduced fertility.

After DBCT was banned in the US because of testicular toxicity, manufacturers continued to sell the chemical to fruit producers in Central America and overseas. Workers in those countries continued to be exposed, and subsequently became infertile.

Another workplace reproductive hazard that came under scrutiny in the 1970s was lead exposure. Scientific studies showed that occupational lead exposures during pregnancy were associated with stillbirth, low birth weight, premature birth and impaired cognitive development of children. Occupational lead exposures were also associated with impaired male fertility and decreased sperm quality.

In more-recent years, there's been increasing effort at identifying the impacts of lower level exposures to a wider variety of environmental agents. At the same time, new information about mechanisms by which environmental agents can compromise fertility in pregnancy outcomes has come to light.

Considerable scientific information has been published addressing particular developmental windows of vulnerability, the fetal origins of adult disease, ways in which environmental agents can alter gene expression – sometimes for life, and across generations – and the impacts of environmental agents on the levels or function of hormones and other signaling molecules, or the impacts on cell division, cell migration and so on.

A robust epidemiologic literature documents a wide variety of environmental agents or contaminants that could increase the risk of infertility, time-to-pregnancy, spontaneous abortion, and birth defects or other manifestations of abnormal development. They include solvents, pesticides, plasticizers, heavy metals and pharmaceuticals. Often at relatively low levels of exposure.

Challenges to further understanding include: non-specificity of endpoints; small but significant increases in relative risks as opposed to dramatic increases, such as we're seeing, for example, with DES or thalidomide; limited or non-existent tracking systems for outcomes and exposures; inaccurate exposure assessments; and complex interactions among a variety of factors, including chemical contaminants, nutritional deficiencies and socio-economic stress, for example.

Yet it is becoming increasingly clear that explicit attention to environmental factors should be routinely incorporated into medical care and public health-policy development at the individual and community level - particularly as it relates to reproductive health and prevention of infertility, reduced fertility, and adverse outcomes of pregnancy.

We're going to be hearing today from infertility research scientists and clinical specialists about how and why they incorporate inquiry into environmental factors into their clinical practice and research. It's my hope that other healthcare professionals who actually see the majority of developing children – teenagers and adults in their reproductive years – will also routinely incorporate questions about environmental risk factors into their practices. In order to become better-informed and to be able to better inform their patients and clients about risks to human reproduction. I'll stop with that. I look forward to hearing what the speakers have to say.

STEVE HEILIG: **Mary Stephenson, MD, MSc** is Professor of Obstetrics/Gynecology and Director of the Recurrent Pregnancy Loss Program, University of Chicago. As of about a year ago, Dr Stephenson began use of an environmental history questionnaire as a part of her patient intake at her clinic for patients suffering repeat pregnancy losses.

MARY STEPHENSON: I'm just going to briefly talk about the questionnaire that we have established. I have a resident who is very interested in environmental toxicology, and we sat down and put together a questionnaire. Presently, our goal is to interview 100 patients with recurrent pregnancy loss – between 2 and 10 miscarriages – and try to get through this lengthy questionnaire for each of the miscarriages.

It is a bit of a fishing expedition. Because where do you start? When we began this project, we looked to the literature to see what kinds of questionnaires had been published. There was little to guide us. Then we pulled a number of articles on possible toxins and pregnancy loss. We did get some help, and I want to acknowledge Warren Foster for helping us with development of this questionnaire.

At the present time, we don't have results. But I just do want to report about – first of all – the interests that my patients have in completing such a questionnaire. We had sent out 100 questionnaires. To date, we have 41 completed. 41 patients completed the questionnaire, and they were very receptive. They answered right away about signing the consent form and calling in and requesting how quickly the resident could set up an interview.

We're primarily looking at occupational exposure. Any contact with heavy metals, organic solvents, different lifestyle choices such as alcohol, caffeine – any drugs, medications. And with recurrent pregnancy-loss patients, we need to also ask about alternative medications or herbalist treatments, or acupuncture. Whatever alternative measures patients use. Exposure to hyperthermia, travel during each and every pregnancy. Hair dyes. We're asking about cosmetic use, and whether any of the products had kohl in it. That's a color additive.

Right now, we're gathering our information. We're hoping to be able to present our preliminary results at the next ASRM meeting. We will continue to complete this questionnaire on 100 patients with recurrent pregnancy loss.

From there, then we will do really a fact-finding mission, trying to focus in on which particular aspects may be associated with recurrent pregnancy loss.

STEVE HEILIG: **Victor Fujimoto, MD** Associate Clinical Professor and Director, UCSF In Vitro

Fertilization Program, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California/San Francisco. With UCSF reproductive epidemiology colleague Mary Croughan, Dr Fujimoto was recently awarded NICHD funding to investigate possible causes for the significantly lower in vitro cycle pregnancy rates he is seeing in his Asian patient population as compared to his overall IVF population - and he has developed a research protocol that includes a seafood questionnaire that is handed out to every new infertility patient for voluntary completion.

VIC FUJIMOTO: Let me start first by giving you a little bit of background on my interest in entering this vast arena. The bottom line is that Dr. Karen Purcell, my 3rd-year fellow, and I decided to look very closely at our experience here at UCSF, with our in-vitro fertilization cycles between the years of 2001 and 2003 - because we have a very high percentage of Asian women going through this program – about 1/3 of our IVF cycles are Asian (female-designated).

With those numbers, we looked very closely, and essentially found that Asian women had about 1/3 less probability of getting pregnant – all other things being equal. Including all the parameters of stimulation and the embryo-quality aspects of this population. Essentially, Asians got pregnant with an odds ratio of 0.69, in our population of IVF patients.

That was a curious finding, to us. So we then contacted Dr. David Granger, who at the time and still is, in charge of the SART research committee. Serendipitously, he had been looking at the SART database over 2 years – from 1999 to 2000, first-cycles only, to look at ethnicity as a possible influence on outcomes in the SART database. As a result of that, he similarly found nationally that Asians had less likelihood of getting pregnant, with an odds ratio of 0.71.

So nationally and locally, we were finding this observation. That manuscript is currently under review for publication. That was really very much – and continued to be – a hypothesis-generating study. One of the hypotheses that has come out of that is, "Is it possible that the environment may adversely affect outcomes... fertility and reproductive outcomes?" In our case, IVF outcomes.

A collaboration began with Dr. Mary Croughan – a reproductive epidemiologist in my division and department. Dr. Jane Hightower – who is an internist in private practice here in San Francisco. She has a passion for looking at mercury effects in adult women and men. Then, Carla Burks-Wicks, M.D – one of our chief residents, currently.

We set forth by developing a seafood questionnaire. This questionnaire now is handed out to every patient who comes through the door -- under the support of our IRB committee here at UCSF.

The challenges of any questionnaire have to do with the length. Our questionnaire is about 10 pages. Details of the questionnaire include ethnicity. We've gone to great lengths to really identify specific nationalities and ethnicities, because of our observations with our populations in the past. We've also included questions about Chinese herbal medicine use. But the bulk of the questionnaire really concerns the consumption of seafood.

Given that – number one – seafood appears to be the primary source of mercury in the US, in terms of bioaccumulation. We've also included shellfish. Questions about shellfish consumption. Because of the fact that shellfish appears to be a major source of another heavy metal – cadmium – in terms of bioaccumulation in the US population. Then we specifically have incorporated into our questionnaire questions regarding sushi consumption.

So we have detailed questions about canned tuna fish consumption, and we have detailed questions about sashimi and sushi consumption. A lot of sushi bars here in San Francisco. To try to understand whether there are any correlations between outcomes here and the answer to the questions that they give, as part of the questionnaire.

STEVE HEILIG: Michael Diamond, MD, Professor and Associate Chair, Obstetrics and Gynecology, Wayne State University and Detroit Hospital. With Dr Julie Wirth in Michigan, who I believe is on the call today, Dr Diamond is co-PI on a 5 year, multicenter clinical investigation into organochlorine exposures in relation to fertility parameters in male infertility patients.

MICHAEL DIAMOND: I have been in Michigan now since 1994. One of the things that I learned when I arrived here that I had not previously been aware of is that there had also been a series of accidents with regard to organochlorine exposures, here in the State of Michigan. As a result, the state government here has been very interested in looking at exposures to these and other environmental agents, as potential concerns for the health of the citizens of Michigan.

This has been studied a great deal in these populations in the past. The issues for maternal child health. Nigel Paneth from Michigan State University. The Jacobsons – a couple here at Wayne State University. George Lambert from New Jersey. Many individuals from the State of Michigan, as well, have been involved in these and other investigations like them.

As a result of interactions with individuals at Michigan State and University of Michigan – which are our sister institutions - over a period of years, we were able to put together the application with Julie Wirth from Michigan State University, who is an epidemiologist and is the PI on it. We've been able to have that funded now by NIEHS. We were specifically looking at the effect of organochlorines on male factor infertility.

One of the reasons we were able to undertake this study is the extensive work that the state has done trying to characterize those exposures. They routinely go out to all the lakes and the rivers throughout the state, as well as the Great Lakes, and sample different fish populations. They have very accurate results now – going back many, many years – depending on which river or which lake, and whether it was the upper branches or the lower branches of a river. And the type of fish, and whether you eat it with or without the skin. They have a good idea of what the body burden from these sport-caught fish is. We also have done heavy-metal analyses on many of these fish.

What we have been doing – now for many years – is looking at the male partners of couples of who come into our clinic. And then more recently also into the clinic of Doug Daly in Grand Rapids. And to assess a variety of factors that might be of interest in male-factor fertility just in general – as well as many specific factors concerning environmental exposures. Whether they be sport-caught fish or whether they be in the workplace or elsewhere.

Through this evaluation, we'll be able to look at the amount of sport-caught fish-ingestion they have, and the level of exposure they've had over time. To then be able to look at that as it relates to their organochlorine levels, as well as a whole host of factors relating to spermatogenesis in these men.

At this point in time, this is not rolled over to something that we're routinely doing as a general part of clinical care in our clinics. That will remain something we would want to do once we had these results and could see what the issues are that we're able to identify.

I think some of the comments that were made earlier will be very important, in that the issues will be whether it'll just be the organochlorines, or perhaps in-combination with other agents that they're being exposed to, which would be having potential effects. How we would be able to try to assess these cumulative effects over time when we're just looking at one time-point. I think that's a challenge that we all will face.

I should also just mention that as part of our work, we are looking now not only at organochlorines, but we are also looking at a series of 12 heavy metals – as well as a variety of phthalate esters from these same populations. We'll be able to compare all of these factors together with the male results.

STEVE HEILIG: We are now at a point where we open it up for discussion. Is **Dr. Joel Evans** on the call? [yes] I have been told that you have a particular perspective. You're an assistant clinical professor of OB-GYN at Albert Einstein College, and author of the *Whole Pregnancy Handbook*. [Also in private practice in CT. Both a traditional practice over the last two decades with patients upstream in their reproductive experience and thinking, as well as a newer practice with patients interested in holistic repro health care.] Do you have any quick reflections on what you've heard so far?

JOEL EVANS: I just want to say that from everything that we've heard with these three speakers is incredibly important, in terms of pushing forward the research agenda. The question of what to do if the patient's pregnant now is something that many of the clinicians have to face today. So I just want to talk a little bit – a minute or so – about what I do. Which is the importance of awareness – starting with a preconception discussion about environmental toxins. Talk about ways to reduce exposures. Specifically, the importance of an organic whole-foods diet. Try to explain the functions of Phase 1 and Phase 2 detoxification systems. Trying to give patients a month or so of detoxification support through various nutrients before they conceive. Going over the latest literature about fetal origin of adult disease. That's in a nutshell what I do with this information, on the frontline with the patient, today.

STEVE HEILIG: Thank you – and I understand you have a book out about this. Are there other practitioners or other people on the call who have a question for one of our speakers?

LINDA GIUDICE: This is Dr Giudice from USFS Dept of Ob-Gyn and Reproductive Sciences. I recently saw a patient who has severe endometriosis and chronic fatigue syndrome, and has had every therapy under the sun for chronic pelvic pain and chronic fatigue. Then we entertained perhaps there might be an etiology in the environment, and the question became how do we assess this? We don't have a questionnaire, yet, for women with endometriosis. We discussed obtaining a body burden study, and also wanted to get a dioxin level. Most clinicians are accustomed to having a major lab slip that you can check off – eg for a blood count, or a thyroid test, etc. There is no such thing for environmental chemicals. It has been an extraordinary challenge to try to find where these studies might be done. I open this to the group as an issue for further consideration, for trying to understand – both in clinical research and in clinical practice, how would we go about considering this type assessment?

SARAH JANSSEN: This is Sarah Jansen from UCSF. We have here – and I know a lot of other universities have – environmental and occupational medicine clinics, where we answer questions all the time about whether a person's condition could be because of an exposure they had either at work or from something in their environment at home or elsewhere. There's an American College of Occupational & Environmental Clinics. You can go to their website, and they can refer you to clinics where people specialize in looking at exposures, and answering complex questions like that.

MICHAEL DIAMOND: Our levels, as of yet, have not been measured. They will be measured by the State of Michigan. It's a LabCorp they have, and they pay by sample. However, they have many, many more samples than they... there's a huge backlog, at this point, in their running those samples. So there's not a resource that I'm aware of that's readily available for clinical use or for clinical research.

ALISON CARLSON: I'm wondering... Mary Stephenson has said that she is [considering the possibility/advisability of developing] a tissue bank. I'm interested...since our speakers have mentioned biospecimen collection...how does that go? What are the challenges there – aside from where you go to get the samples tested? I mean in terms of collection, and finding out *what* you should collect?

MARY STEPHENSON: That's all been something I've been thinking about for the last year now. Certainly, you'd also have to take into account the costs associated with collecting serum, plasma... Would we use PAX genes for RNA? DNA extraction? Urine? Ideally, we would want to collect all of those specimens and store them for future use. But there would a tremendous cost involved in doing all of that. But that would be the goal. Then, to look to the future on specifically measuring the heavy metals or dioxins – whatever.

CARLSON: But what kind of process is it to try to... Vic [Fujimoto] has described a specific hypothesis. Mary has more of a broader fact-finding mission, as you said. But I meant...there must be a lot of challenges in trying to figure out for a specific patient group or study, what kind of sample is right to collect for what (and if Shanna Swan is on the call maybe she could comment). I know that gets complicated. I'm just interested in if this is a small or a big undertaking.

DIAMOND: It's a huge undertaking. We are collecting specimens from our patients that are participating in this NIEHS-funded study, or RNA analysis from the sperm. That is not actually part of our grant, but something that we are doing with these specimens. But it requires dedicated individuals who are available to process these specimens, and make sure that there's good quality control. Making sure they're stored well and that you don't lose power and lose everything in your freezer. Another *huge* issue is IRBs. We have a tissue bank which actually was acquired for studying post-surgical adhesions and endometriosis. But the IRB process is another component of what has to be gone through in patients giving you for-consent of storage of these specimens. There may very well be issues with subsequently sharing them with other investigators. Depending on how your IRB is written, and what your institution will allow. It requires lots of time. And as Mary Stevenson was saying, if you're just doing it as an exploratory stage, the expenses are ones for which there are not good resources that are easily found to cover. So you end up having to take funds from other sources that you have – scanty as they are, in this day and age – to try to accomplish this. Hopefully, then to have some preliminary data for a more hypothesis-driven application in the future.

GAYLE WINDHAM [CA DHS]: I agree. I think it raises a lot of issues when you're talking about an individual clinic patient. What would the dioxin level tell you? And then what could you do about it? That's sort of an immediate ramification. Let alone that they're very expensive to run. Many of these things are run at CDC or state labs, and they're doing them for studies. Of course, if there's money to be made, a commercial lab might get involved. But at this point, I think that's hard to find.

STEPHENSON: It was interesting in our IRBs for the questionnaires that we're applying to our recurrent-loss patients...They made it very clear that we were not allowed to ask any questions about environmental exposures to any pregnancies that were in-progress. We could only ask about prior. They made quite a deal about that.

HEILIG: Do you have any speculation as to why? That structure?

STEPHENSON: No. I was really quite surprised by their adamant statement about that.

WINDHAM: But what do you do about it? Because the dioxin's been there for years. Then there's no... You can't give them advice how to get rid of it.

HEILIG: Though part of this *is* the research part, or context.

SHANNA SWAN (U of Rochester): Yes. I wanted to support what Gayle Windham was saying. Just to step back a little bit, and be careful that we don't unnecessarily frighten people. Because while the links are interesting on a population level for a number of these chemicals, we do not have very strong data about most of them that links them on an individual basis to fertility or infertility. So I'm not sure that it's justified to get ... A dioxin level costs \$2,000 a pop. That's not going to be something that people can do. Like Gayle says, what would they do with that information, anyway? I think we really have to separate the information that we're getting for epidemiological and research purposes, from what we're telling patients. I'm very concerned that people get unduly panicked about what their... Do we really need to detoxify everybody? I don't think we have the evidence for that. So I am just trying to insert a word of caution, here.

HEILIG: Right. Perhaps – I wonder if anybody has been involved, yet – or has any ideas about doing this on a more population level, with biomonitoring studies, and so forth

SWAN: There are many, many studies. *We* do them. Lots of people do them. Those are going on, all the time. The information is coming out. But it's not at the level of where we can apply it on a clinical level.

SHERRY SELEVAN (recently ret. US EPA, NIOSH): If you look at the NCHS website – part of CDC – they have an exposure report. It's population-based samples. They have a lot of the different kinds of exposures that people are interested in, you can at least see what the baseline is like for the US.

SALIM DAYA (McMaster Univ): Just to add to this discussion: The issue of PCB exposure has been raised in the past. A study was done comparing different populations. It was an ecological study. They were looking at the Great Lakes region compared to an area in Calgary, where there is less pollution. In order to really be able to get a handle on the PCB levels, in addition to blood, fatty tissue had to be taken from the umbilicus at the time of a laparoscopy, to be able to quantify the levels in the females. With that approach, it was evident that high levels are associated with fertilization problems. But it requires more than just blood.

DORI KNOFF (Endometriosis Assn): My question is a general one. We would like to add at some point in the future survey questions on exposures for women with endometriosis. Of course, there's always that problem with recall, in terms of some of the women completing the surveys who are older. How do you deal with recall, as far as formatting the questions?

STEPHENSON: Recall bias is our biggest obstacle to overcome. When you're doing a questionnaire, I think you need to think carefully about if the patient is going to fill out the questionnaire... Are you going to have a dedicated person asking the same question in exactly the same way? Or – in our case – for each pregnancy, even having – in addition to recall biases, you have 2 different people

administering the questionnaire. You may get differences in the way they ask the questions. So, it is a real problem. Especially, trying to remember, "Well, 6 pregnancies ago, how much fish did I eat in a week?"

FUJIMOTO: The recall issue is definitely a serious issue. Epidemiologists who spend a lot of time designing questionnaires clearly understand that recall bias is one of the obstacles that goes into this equation, when you start trying to ask retrospective questions. I'm not aware of any clear or easy way to get around the recall bias. Mike – do you have any thoughts on that issue, in your experience?

DIAMOND: It definitely is something we've been very concerned about. It's been very interesting to me, as our coordinators talk to the men in our study, how *well* they remember their fishing activities. They know the family cabin is on a certain lake, and that's where they've gone...It seems to be remembered much better than most other activities. But nonetheless, it remains an issue which is very hard to validate.

TED SCHESSLER: I'm wondering, Vic: Are you measuring mercury levels in your patients, as well as doing a questionnaire?

FUJIMOTO: Here gets to the question Shanna Swan brought up. I have, actually, on a clinical level. I've tried to address mercury levels – just as Jane Hightower has in her population of internal medicine patients. But I have the same issues ...I see some pretty high mercury levels. But there are several issues with that. First, if you go to a standard lab requisition, then obviously, the issue of where that mercury level assay is run comes into question. When you have these nationalized LabQuest and LabCorp and these sort of large consumer-driven clinical lab systems, it's very difficult to get a very clear handle on where they actually go to have their mercury levels checked. It may ultimately be multiple sites – depending on the region of the country. There are many facets. It's not always easy to get a clear answer. Essentially, that has left me with the undertaking of basically doing a prospective study – looking at all of my patients, both Asian and Caucasian. And to collaborate with NICHD and the CDC to basically do a prospective collection of blood, urine and follicular and seminal fluids. All with the goal of trying to identify heavy metals within the population that I serve here.

Again, I think you have to look very closely at the region. As Mike said, there are some very unique aspects of the various parts of this country, and the bodies of water that we are surrounded by, that may – in some part – influence the types of things that we want to look for, from an environmental-contamination standpoint. I can tell you that the San Francisco Bay is particularly high in heavy metals. Specifically, mercury, cadmium and lead. In fact, my collaboration – and hopefully, funding – for this prospective IVF study will involve looking at those three heavy metals.

We just need to understand what is going on here, long before we can start to *recommend* that we check levels. Because we don't know how to interpret what we get. I think that holds true with the dioxin question. I think that holds true with any heavy metal or PCB or anything else that we decide to order. With one patient, I had thought about checking a PCB level. But that's thousands of dollars. I'm not sure that I can justify getting that – even if the patient were willing to pay for it on her own. And how to interpret that is ultimately the next question. We have no idea.

HEILIG: On that note, I'm going to guess that mercury is probably the most-common question. But in patients in general, what are – for our speakers – what are the most-common environmentally related questions you get?

SWAN: I wanted to[make a point and] ask a couple of questions. I do think this finding on the Asian population is fascinating. [But] I'm wondering a couple of things. There are two large mercury-exposed cohorts. One is in the Seychelles, and one is in the Faroe Islands. The Seychelles population is not contaminated by PCB. So you get a clear... (And that's out of Rochester. So I know a lot about it, because I'm here, now.) But they have not found any adverse effects of mercury. I just have to tell you that. They haven't looked at fertility, but as far as cognition – they don't [find effects] and they have a very highly exposed population. The Seychelles, on the other hand, *have* found adverse effects. But they also haven't (I don't think) looked at fertility. So one thing would be to talk to those studies and see whether they can give some information.

The other thing I'm wondering about is whether the National Survey for Family Growth has information by ethnicity on fecundity or delayed conception, and whether they see the same differences nationally – to see whether it's a local, San Francisco problem. The third thing is, to look at Asians by 1st and 2nd generations.

FUJIMOTO: So, I've initiated a broader database type of study – and at this point, it's retrospective. But it is really to look at fecundity issues, treatment outcomes, with anything that we can provide for patients. And really exploring a larger database to see - our database - to see whether these sorts of issues are relevant. But I think your point of 1st-generation and 2nd-generation is important to clarify. I think within the Asian population, it's important to understand nationalities and the potential differences in socio, cultural and dietary habits that are prevalent, even within a self-described Asian population - where an Indian population may have a very different diet and consumption levels than a Japanese or a Chinese family.

CARLSON: I'd like to pick up on the question Steve Heilig just asked. It got a little bit buried. It attends to a sort of a big-picture conclusion I'm drawing, here. From the speakers so far, I'm getting the message that right now we're at a stage where we're ready to promote environmental history-taking in clinical research settings. But there seem to be some differing feelings [in regard to clinical practice]. For instance, Joel Evans might have reacted differently to Shawna Swan's points today? So, how ready are we to be dealing with environmental histories in purely clinical settings? Steve asked how the speakers ultimately deal with specific environmental-risk questions or requests for advise from patients that [clinical research] intake questionnaires might raise? What are the typical concerns of patients? I'm just interested in how do clinicians who are delving into this realm handle the environmental risk question?

HEILIG: Right. And with regard to the context of the cost of it and the uncertainties about how to both interpret and to provide some kind of intervention.

FUJIMOTO: I've gotten a lot of questionnaires back on my patients. Point one is that for the female populations we serve, in general, this is a very intriguing and fascinating area for them. They want the power of understanding what it is about their surroundings that might impact their health in a negative fashion. I think there's that part that drives them to answer these questionnaires relatively easily. I've set up my questionnaire in a way that makes it very simple and easy for them to define whether they're a fish-eater or not. And when I start asking questions about sushi consumption, sashimi consumption and tuna fish consumption... I try to be as detailed as I can in the questions that I ask them, to jog their memories. But in looking at some of the 100+ questionnaires that I've gotten back, I think it's usually really a an all-or-none phenomenon, here. You either love fish, or you don't.

CARLSON: Vic, thanks for that. But I'm still curious... Joel Evans said that in his *practice*, he is *proactive* in sharing information. I was wondering how practitioners in the upstream reproductive practices deal with the uncertainties [about the evidence].

FUJIMOTO: My questionnaire is under an IRB protocol. We decided to do it that way because we really wanted to set it up in a study fashion as part of a much larger, broader study – to address the study of environmental contamination and reproductive fecundity. So it's not a standard part of a clinical questionnaire that we give out.

STEPHENSON: The same in my practice. Our questionnaire is under an IRB. I think that with recurrent pregnancy-loss patients, many of them come in with guilt about, "What if I hadn't eaten that or gone there...?" Or done this or that...I think it's very important not to increase that anxiety or guilt. We need to be very careful about how we word such questions.

FUJIMOTO: I think if you don't do it under an IRB protocol, the risk you run is the bias that you give to the patient, to make them think that somehow by asking these questions upfront, before they even see you, as part of your standard medical questionnaire – that means that the bias is already clear to them. That they need to stop doing... That [if] this is not presented as part of a larger study, and the fact that we don't really know the answer to these questions, then you're essentially telling the patients that they need to stop their fish-consumption behavior. And I'm not sure that's necessarily the case.

JIMMY SPEAROW (UC Davis): I'm just wondering if you're banking DNA and looking at the mercury stability...those kinds of questions in terms of other genotype...things such as Glutathione S-Transferase, alleles, etc, etc.. Or at least being able to look at those in the future, to really discriminate between individuals who are more affected versus less affected by a given exposure.

DIAMOND: Yes, we are. That's part of our protocol, actually – to look at a whole series of different polymorphisms.

SPEAROW: But what I'm saying is, that should really be encouraged by all these studies, if at all possible.

ANNE GREENLEE (Oregon Health & Sciences University): My question is for Mary Stephenson. I'm wondering about the cosmetic use of kohl. What is kohl?

STEPHENSON: It is a color additive that is in some cosmetics. As I recall, the color additive is primarily in products that are made in Southeast Asia. There are limited reports of association with reproductive loss.

HEILIG: It's extremely common in the Indian subcontinent. We're coming up on the time, here – unless there are remaining remarks? I'm going to turn it back to Alison to mention the conference in January, perhaps.

CARLSON: Mentioned earlier, the summit is scheduled for January 28th through 30th 2007 at UCSF's Mission Bay Conference. We'll be getting more information out on that, so please mark your calendars. Thanks to all the speakers and participants for taking the time to be on this call. I will be getting in touch about our next quarterly teleconference. There will be an audio recording and transcript of this call posted on CHE Fertility's webpage before long.