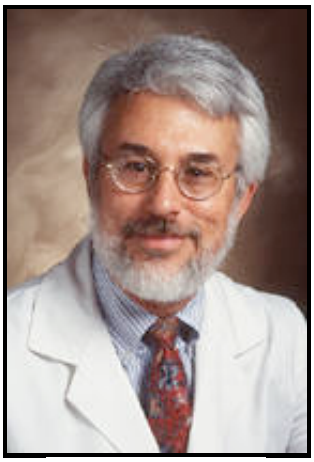
12th Annual Conference on Polycystic Kidney Disease, June 2001. Selected Talks.

Web presentation sponsored by an unrestricted educational grant from Sigma-Tau Pharmaceuticals

Polycystic Liver Disease
Part Two of Two



Dr. Ron Perrone

Ronald D. Perrone, M.D.
Professor of Medicine, Tufts University School of Medicine, Associate Chief, Division of Nephrology, Associate Medical Director of the Kidney Transplant Program in New England Medical Center in Boston, Massachusetts.

CME-related Information

This talk is not presently accredited for Category 1.0 CME credit.

Program Objectives and Goals: The primary target audience is nephrology health care professionals. The educational objective is to understand the genetics of PKD as it pertains to liver cysts. Further goals are to understand the prevalence of liver cysts in PKD patients, the most common clinical problems that these cysts engender, and potential treatment options. Posting date: November 3, 2001.

No post-test nor evaluation form at present

Disclosure Statement: Dr. Perrone discloses no support relevant to the material being discussed. Web extension of this symposium is being provided through an unrestricted educational grant from Sigma Tau, Inc.
About the Speaker: Dr. Ronald D. Perrone, M.D. is Professor of Medicine, Tufts University School of Medicine, Associate Chief, Division of Nephrology, Associate Medical Director of the Kidney Transplant Program in New England Medical Center in Boston, Massachusetts.
HDCN CME Policies: See **this page**.

Listen to this Lecture using the Real Player

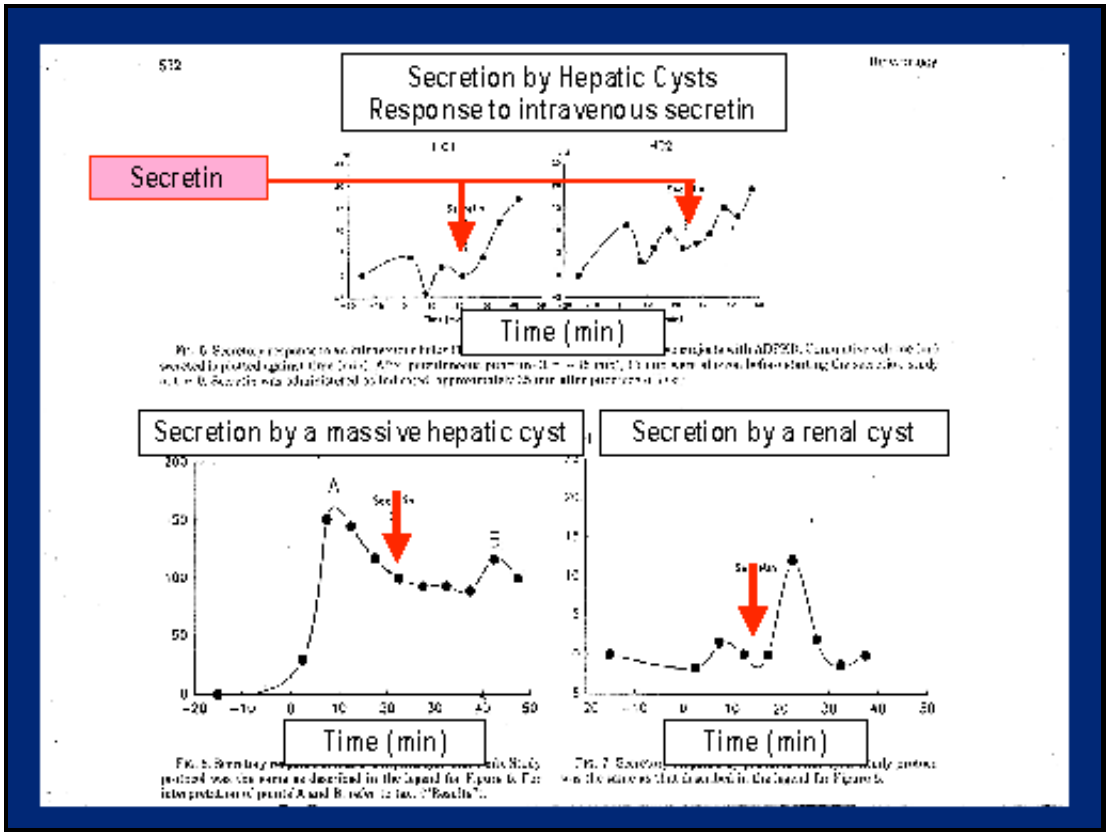
You can scroll through the talk while listening to the audio. You won't be able to

listen to these files if you have not downloaded and configured the Real Player (the Real Player is free). Make sure that View - Preferences - Content - Enable Automatic Links is checked.

Click on the podium to start the talk.

To download free the Real Player click here. You may have to search a bit to find the link to the FREE player.

00:00

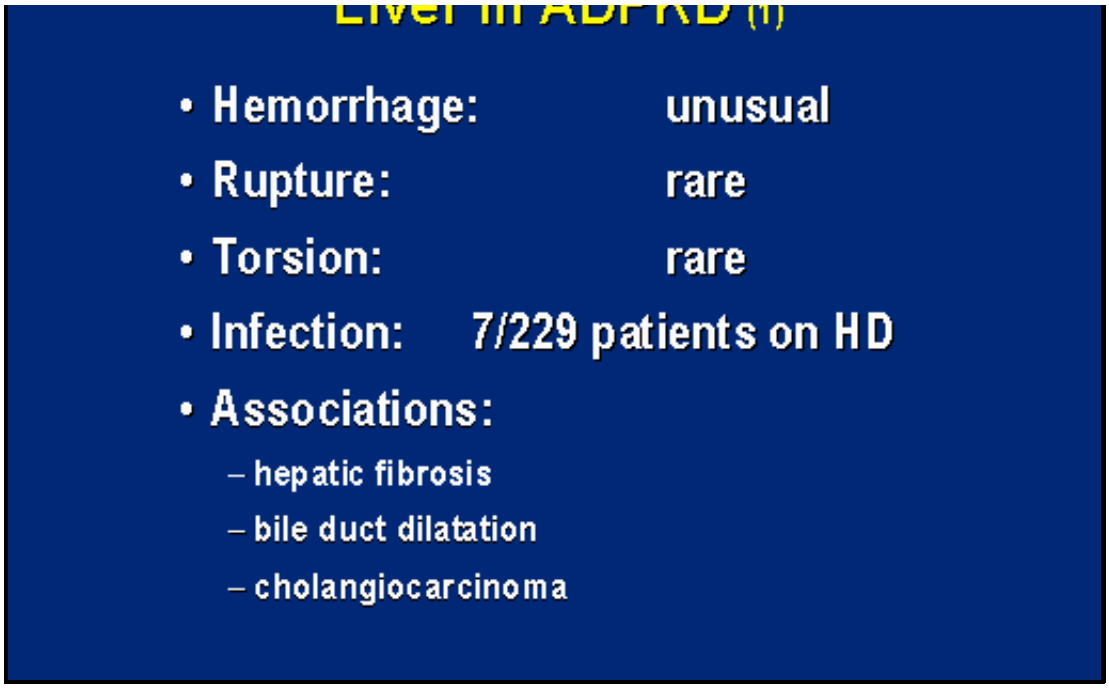


Source: Everson GT et al, Hepatology. 1990 Apr;11(4):557-65.

Response of liver cysts to the hormone secretin
If you study liver cysts from a patient with PKD, the same exact thing happens. This is a study done by the Denver group. What they did in patients with polycystic liver cysts, they put a tube right into the stem of the cyst and measured the amount of secretion that was taking place. Then they gave that hormone, secretin, which you make after you eat a meal. Lo and behold, the cystic epithelia did the same thing that the normal bile duct did; that is, it made more fluid. This possibly could account for some of the symptoms that people might get after a meal, when secretin is made and there might be more secretion of fluid into the cysts and more pain and discomfort that could occur.

That is all I am going to say about the formation and the function and the basic science of cysts. I am now going to switch over to clinical aspects of liver cysts in polycystic kidney disease.

00:00

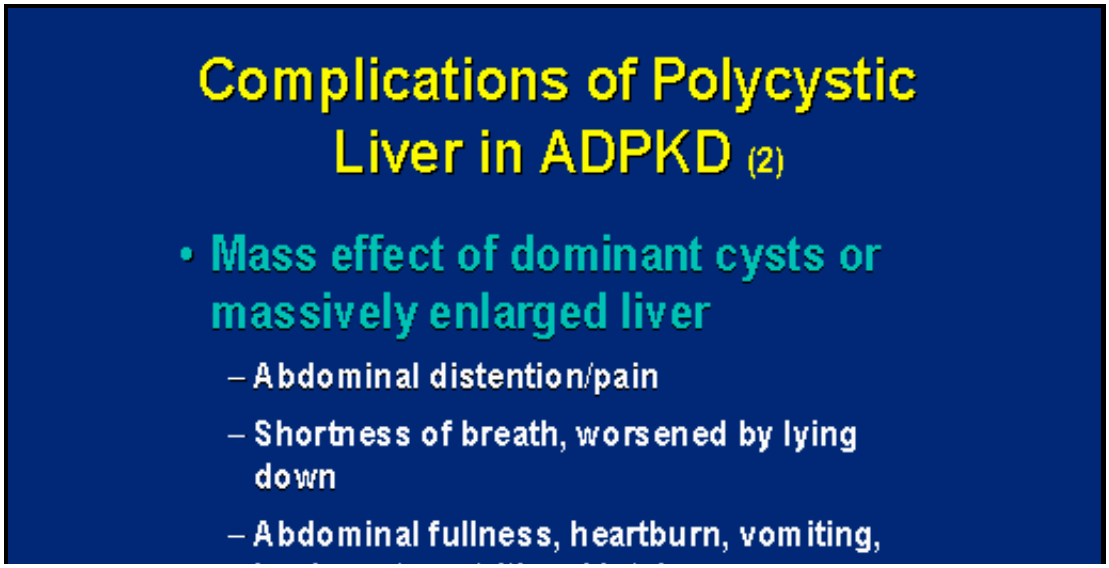


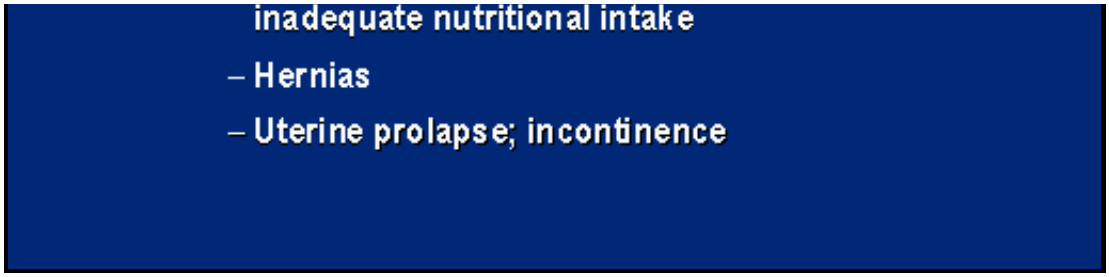
Complications of a polycystic liver in ADPKD
I am always a little uncomfortable talking to patient groups about complications and death and dying. I will mention that these are things that don't affect most individuals and that there are treatments and therapies and diagnostic procedures for that. I will try to present honest information, but recognize that most of these things can be diagnosed and treated and solved.

Just like kidney cysts, liver cysts can hemorrhage. They can rupture--that means break open, which when it happens is a very painful episode. Torsion means that they can twist. You can imagine that the cystic liver is very heavy, and it is not anchored sufficiently to keep it in place. Sometimes cysts or structures can move around and cause discomfort.

Again, just like in the kidney, infection of a liver cyst can take place. However, in the liver, a cyst cannot get infected from the outside because there is no connection to the outside. So it usually has to become infected through the blood stream. In one study, liver cyst infection was reported in 7 out of 229 patients on dialysis; so around 3 percent of the patients on dialysis had a liver cyst infection in this one study. The other things that I mentioned earlier--the liver fibrosis, the dilatation or the enlargement of the bile duct, and the rare complication of cholangiocarcinoma.

00:00





Mass effects of liver cysts in ADPKD
How else can the liver cysts cause difficulty? One can have this very large cystic liver which then presses on other structures in the abdomen and causes symptoms by virtue of just being a much larger organ. Abdominal distention just means swelling of the abdomen and pain; shortness of breath which is worsened by lying down, and that happens because the large liver is pressing on the diaphragm, preventing it from moving normally. The diaphragm is the muscle that helps your breathing.

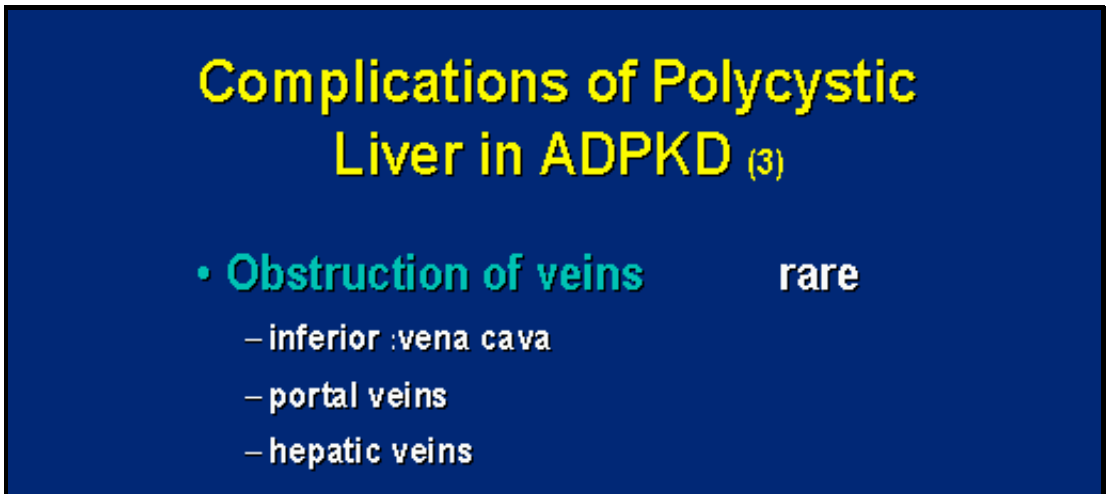
Abdominal fullness, heartburn because again the stomach is compressed and the acid comes back up, vomiting, and in some individuals an inadequate nutritional intake just because they don't have room to eat a full meal. Their symptoms prevent them from eating a full meal. Hernias are one of the connective tissue abnormalities of polycystic kidney disease and reflect a weakening of the normal muscle or tissue structure.

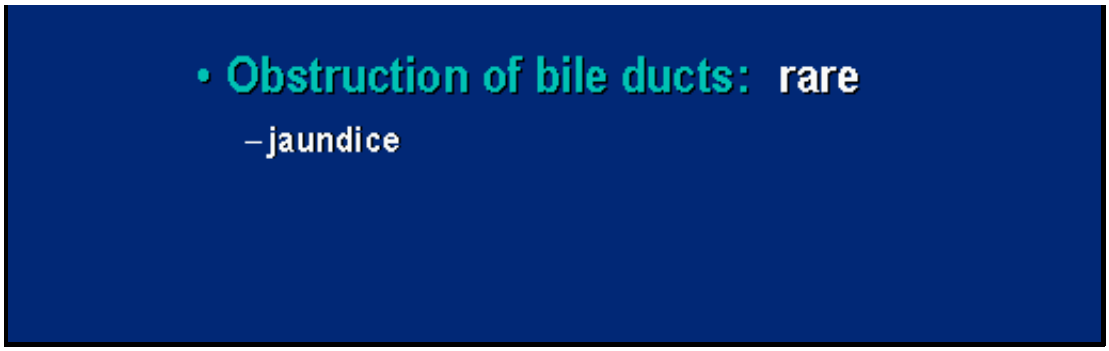
If you have a very large cystic liver and two large cystic kidneys, that puts a lot of pressure on the abdominal wall and the formation of hernias is not surprising when that happens. Uterine prolapse...when women have had multiple children, after they lose estrogen the supporting structures are not as supporting. So what we call pelvic relaxation--loss of bladder support, the uterus can protrude, and difficulty with bladder function can occur. These can occur normally, and these are exacerbated or made worse by the very large cystic liver and cystic kidneys.

Audience member: I have a question right here. Is there anything that you would recommend giving so that you can rest better at night?

Dr. Perrone: Is there anything that can be given to help someone rest better at night? In general I don't like to use a lot of sleeping medication or pain pills, but clearly if someone is having a lot of symptoms, that would certainly be reasonable. We try to limit those to use at night so that you're not dragging around during the day. I think the other thing is to try to find a position that one is most comfortable in. You have more experience with that than I do, certainly. I don't know if elevating the head of the bed, for example... it certainly would help with heartburn, but it may or may not help an individual. There aren't really any drugs or agents that we know of that will reduce the size of the liver cysts. I could perhaps talk about that more at the end of the discussion.

00:00

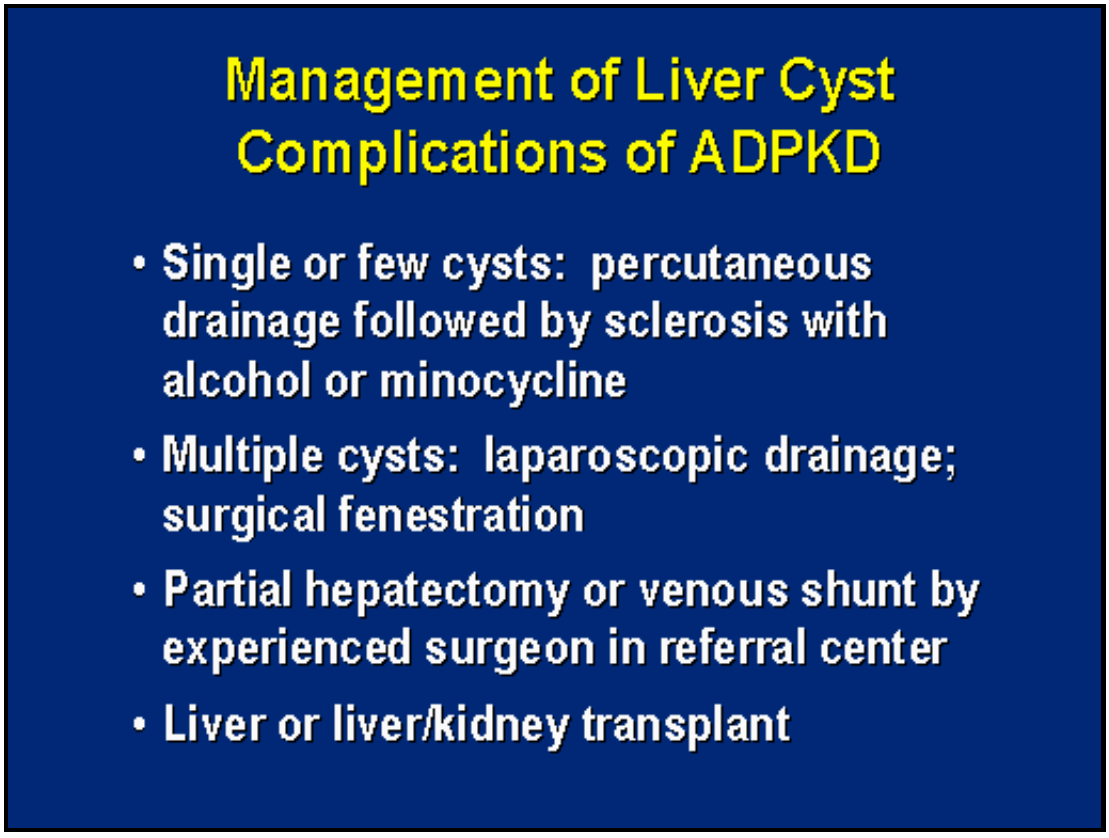




Effects on the vena cava and bile ducts
The other thing is if the liver gets very large, you can press on some of the veins that are within the abdominal cavity. The inferior vena cava is the large vein that drains the whole lower half of the body. A very large cystic liver can actually block this. The vena cava goes up right next to the aorta in the back. That certainly can occur. Then the portal and the hepatic veins are the veins... the portal vein going from the bowel to the liver, the hepatic vein draining the liver. A large cystic liver can compress those, also.

Obstruction of the bile ducts--I showed you that cysts came from the small bile ducts, and it is possible that if a cyst enlarges it can block one of the bile ducts within the liver. If it blocks the main bile duct, it can cause jaundice.

00:00



Management of liver cyst complications in ADPKD
How do we manage these potential complications? As I indicated, most of them are uncommon. I see a lot of patients with polycystic kidney disease and I see very few who have had severe or ongoing liver cyst problems. If the problem is caused by a single cyst that happens to be pressing on something or a few cysts, modern imaging and draining techniques are such that it is possible to take care of this without an operation. Percutaneous drainage means putting in a needle, usually under CAT scan guidance, into the cyst and draining it. Then you can inject an agent that causes scarring, either alcohol or minocycline, which is a tetracycline- type drug. So if there is a blockage or a hemorrhage or

something causing an acutely painful problem, using a CAT scan and needles put in through the skin, you can usually deal with these.

For a problem that is caused by multiple cysts, again there are now many surgical techniques using a laparoscope, which is one of those fiberoptic scopes that can be used to take out gallbladders and such... this can be used to intervene and deal with multiple cysts, again without requiring a major abdominal procedure. I would suspect most medical centers and probably even a lot of community hospitals now have the techniques for percutaneous drainage. I don't think they all have someone who is skilled at a laparoscopic surgical approach. Even if someone has taken out a gallbladder using a laparoscope, it doesn't mean that they are going to be good at dealing with cystic livers or kidneys. Surgical fenestration means actually having an open surgical procedure. The surgeon goes and cuts the roofs off the cysts. So instead of having fluid build up in them, they just drain freely into the abdomen.

Audience member: Is that good?

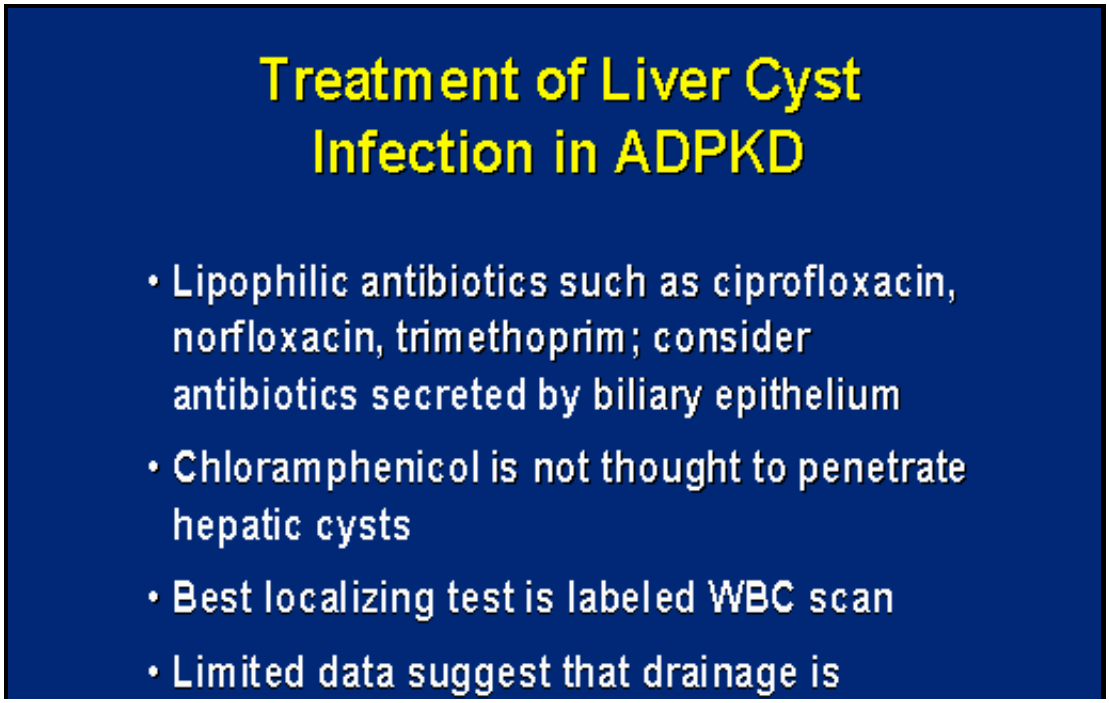
Dr. Perrone: The question is, "Is that good?" It depends on what the problem is. But in general, a small operation is always better than a bigger operation.

Audience member: Allowing the fluid to drain?

Dr. Perrone: The question is, "Is unroofing a cyst and allowing it to drain in the rest of the abdomen a good thing?" You only do it to solve the primary problem. So you wouldn't do it without a real reason. There are some issues with fluid build up in the abdomen after major liver surgery, major cyst removal. I think this really has to be looked at very individually for the specific problem in the specific individual. Again this isn't something you have done in your local community hospital.

I will talk in a moment about what we call massive polycystic liver disease. Partial hepatectomy means partial removal of the liver if there is blockage of the veins or venous shunt. This is something that is only done by an experienced surgeon in a referral center. Again, you want someone who is very experienced with liver surgery and liver transplant and such before you would allow anything like this to take place. Again, for massive polycystic liver disease that I will talk about in a few minutes, there are some individuals who have undergone liver transplant or combined liver and kidney transplant to solve this problem. That is really only a last resort. We will talk more about that.

00:00



Infection of a liver cyst in a patient with ADPKD
Liver cyst infection is a special case, just as is kidney cyst infection. It is important to recognize that the treatment isn't identical. We have known for years that for kidney cyst infection you have to use certain antibiotics. Lipophilic means that the antibiotics pass through fat, which means that it is easier for them to penetrate through the cyst walls, rather than antibiotics which are just water soluble.

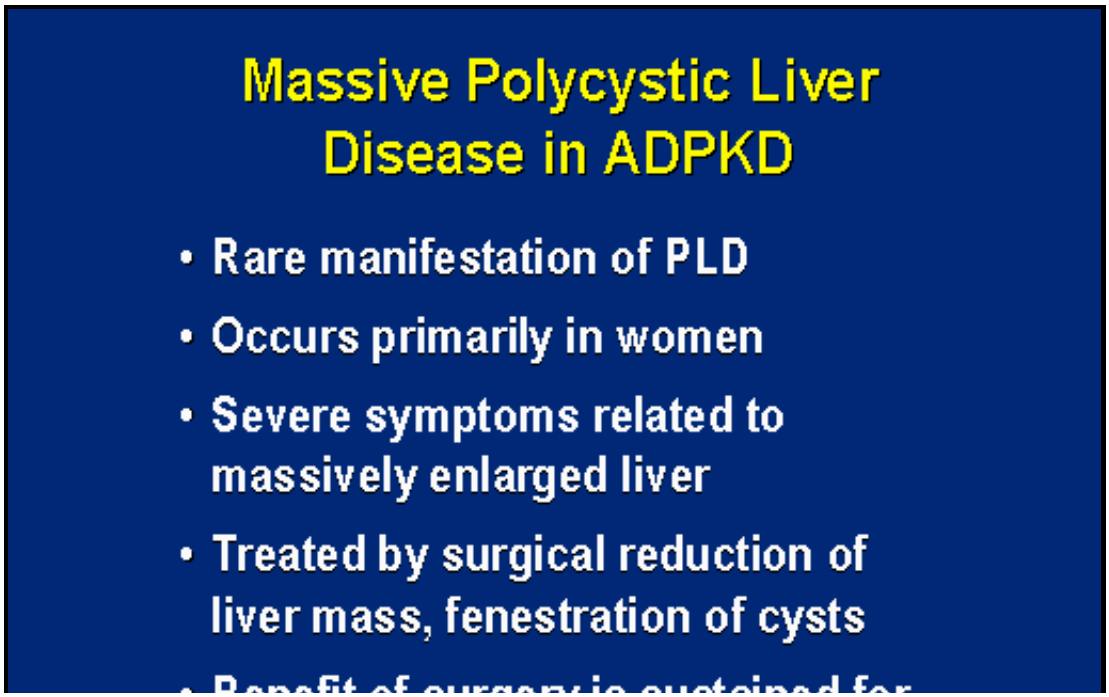
We have known for years that you have to use special antibiotics for kidney cyst infection. In addition because the bile duct secretes things, it does actually concentrate some antibiotics there. So there are some antibiotics that are specially used for what we call "angiitis", which is a bile duct infection or gallbladder infection, which you would use in a liver cyst infection. Chloramphenicol, which is one of the mainstays for kidney cyst infection, doesn't get into liver cysts. These are tough to diagnose because when you have abdominal pain and you have cystic kidneys and a cystic liver, anything is possible. You could have a cyst infection in the kidney, you could have a cyst infection in the liver, you could have a kidney stone, you could have an acute gallbladder attack. The doctor needs to think about this fairly carefully and look hard and make the appropriate diagnostic endeavors.

This morning in the limited literature review, there it suggests that the best localizing test is a labeled white blood cell scan. What that means is they take white blood cells from the individual with the infection. They label the white blood cells with a radioactive marker; inject them back into the patient; and when these cells congregate in the area where the infection is, they can take a picture of this and localize it (the infection).

The other point I would make, again with limited data; there is limited data in the literature that suggests that draining of a liver cyst infection is very important, whereas a kidney cyst infection doesn't necessarily have to be drained. Again with the techniques that we have now, with CT-guided imaging, most of these cysts can be drained without requiring an operation. But it is important that that be done. The outcome of these infections in patients who didn't have them drained was not as good.

Again, diagnostic efforts, appropriate antibiotics, and then drainage for a liver cyst infection.

00:00



Massive polycystic liver disease in ADPKD
A few words about massive polycystic liver disease in PKD. This is a very rare manifestation of polycystic liver disease in PKD. I suspect in this room we probably have the largest number of people with PKD in one place. It occurs primarily in women. The severe symptoms are related to the... yes?

Audience member: Could you just clarify... is that the same as hepato- megaly?

Dr. Perrone: The question is.... hepatomegaly is actually just a generic word for an enlarged liver. The liver can be enlarged for any reason.

The symptoms relate to the massively enlarged liver. This is treated by surgical reduction of liver mass and fenestration of cysts, the unroofing of cysts that I mentioned. I guess Dr. Torres' group at the Mayo Clinic has the most experience with this, at least the most published experience. They have demonstrated that the benefit of surgery is sustained for at least five to eight years. That is, it is not something that you do and it comes right back. Again, this is very specialized surgery. Even many major academic teaching hospitals don't necessarily have experience with this. If you are thinking of undergoing anything like this, you really want to seek out or at least get a second opinion from a place with a lot of expertise.

Audience member: What is the criteria for a massive liver centimeter-wise?

Dr. Perrone: The question is, "What is the criteria for a massive polycystic liver by size?" I don't know if there is an exact cut- off for size. Certainly I would define it as one that is causing substantial symptoms and interference with quality of life. Remember in an individual who is small and thin, they might have more symptoms than someone who is larger with a different size liver.

00:00

A massive polycystic liver
This is a picture of one of Dr. Torres' patients during the operation. This is certainly one of the biggest polycystic livrs that I've ever seen. What they do is they find that part of the liver is just cystic and they can remove that part. They try to leave the normal liver tissue alone.

00:00

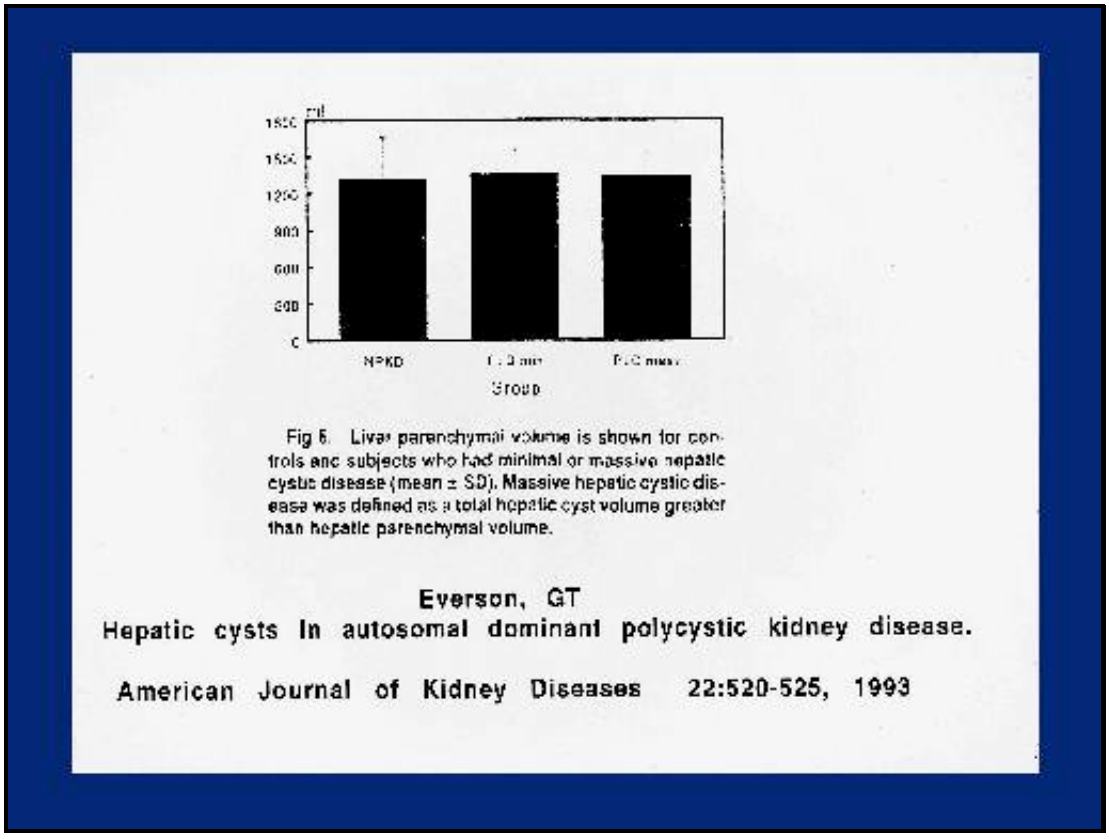


Fig 5. Liver parenchymal volume is shown for controls and subjects who had minimal or massive hepatic cystic disease (mean ± SD). Massive hepatic cystic disease was defined as a total hepatic cyst volume greater than hepatic parenchymal volume.

Source: Everson GT. Am J Kidney Dis. 1993 Oct;22(4):520-5. No abstract available.

Makeup of a liver with polycystic liver disease
What is interesting is that if you study these patients in detail, and this is a study done from the Colorado group... what they did is they took CAT scans and just took multiple sections of people's livers who had massive polycystic liver disease. They were able to count out how much of the tissue was normal liver and how much was cyst. What they showed is that... this is NPKD, this is family members of PKD patients, and this is the amount of normal liver tissue. These are individuals who had minimal or mild polycystic liver disease. You can see there was no difference in the amount of normal liver tissue.

This third bar refers to those people who had massive polycystic liver disease. It turns out that they have a normal amount of liver tissue. The increased size is made up solely by these cysts that don't seem to be affecting the function of the normal liver tissue. We know that people with polycystic liver disease in PKD don't suffer from liver failure. That is the liver function by every means that you can assess it is completely normal. This study demonstrates that the amount of liver tissue, other than the cysts that are there, is also completely normal. That is a significant difference from polycystic kidney disease where the function of the kidney is lost.

00:00

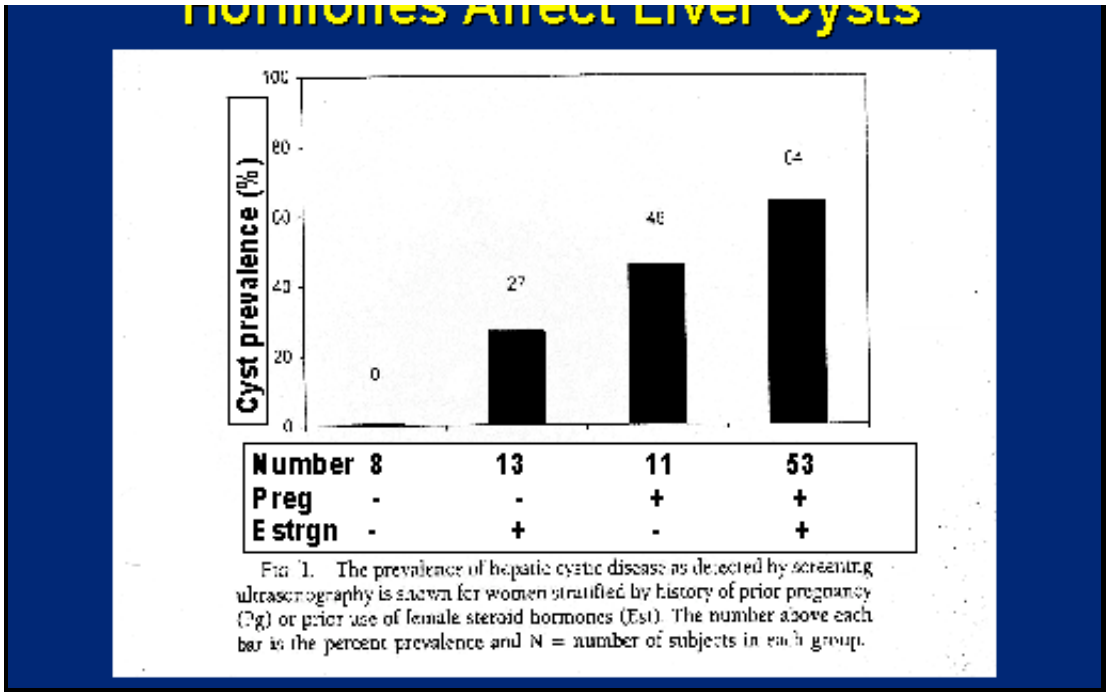


Fig. 1. The prevalence of hepatic cystic disease as detected by screening ultrasonography is shown for women stratified by history of prior pregnancy (Pg) or prior use of female steroid hormones (Est). The number above each bar is the percent prevalence and N = number of subjects in each group.

Source: Sherstha R et al, Hepatology. 1997 Nov;26(5):1282-6.

The effect of female hormones on liver cysts

I mentioned that this is primarily a disease of women, and I did want to talk about estrogens and pregnancy. I am sure there will be a lot of questions about that. This is a study looking at the prevalence of cysts, which means whether you have cysts or not. This is women who have either been exposed or not exposed to pregnancy or estrogen. You can see in these eight women who were never pregnant, never had estrogens, had virtually no liver cyst disease. The next group had never been pregnant but had been exposed to estrogens, about a 30 percent prevalence of liver cyst disease. Pregnancy with no estrogens is higher. With both, it is a double whammy--almost 70 percent have liver cyst disease. I didn't bring them, but there are other data from the same study showing that the greater the exposure to estrogens and the more pregnancies, the more severe the liver cyst disease.

Audience member: What about birth control pills?

Dr. Perrone: They would be included under this exposure to estrogens. Unfortunately in many of these studies, it is not possible to determine precisely what people took and over what period of time because they are done in individuals who are in their 40s and 50s and over who may not remember exactly what they had taken.

Audience member: Is there a difference between pregnancies carried to term and terminated pregnancies?

Dr. Perrone: The question is, "Is there a difference between pregnancies carried to term and pregnancies that were shortened?" I don't know the answer to that. I suspect that the full-term pregnancies would have more of an estrogen effect than the shorter pregnancies. But many women with PKD have been pregnant and don't have severe liver cyst disease.

Audience member: What about the use of phytoestrogens, such as soy products?

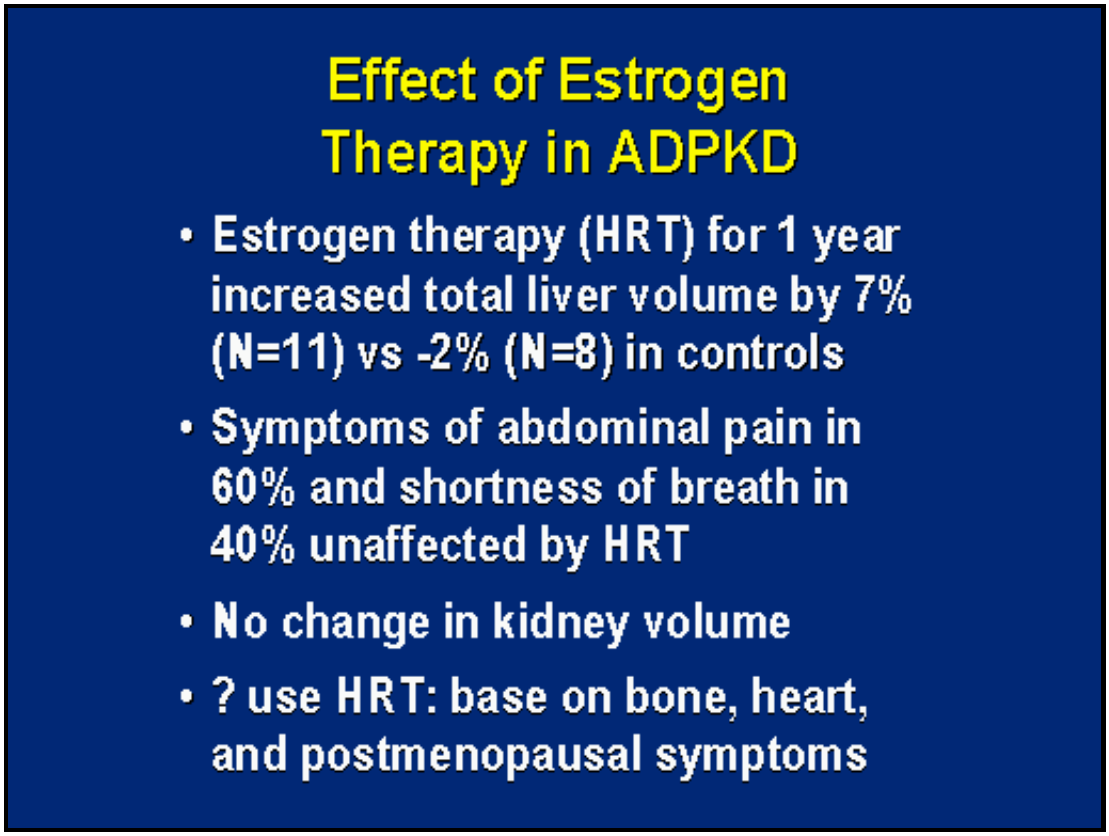
Dr. Perrone: The question is the use of phytoestrogens, the soy proteins that have an estrogen-like effect. There is no data on that to my knowledge.

Audience member: What about use of the transdermal patch instead of oral estrogens?

Dr. Perrone: The question is, "What about use of the transdermal patch instead of oral estrogens?" The transdermal patch is a way of giving estrogen that avoids sending the

estrogen directly to the liver. When you ingest food or take a pill, it is absorbed and goes into the circulation that goes right to the liver. So it has been proposed that a transdermal estrogen, like a patch that you put on the skin, since it bypasses the liver is a safer way to go. That certainly makes sense, but no one has done any studies on it to say that definitely this is the way to go or not.

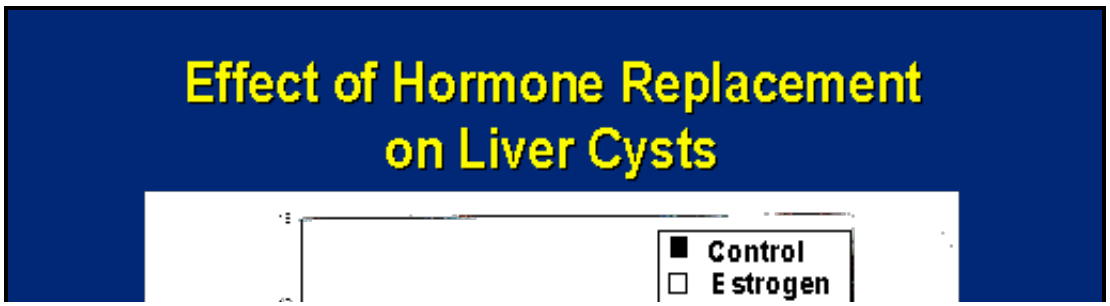
00:00



Source: Sherstha R et al, Hepatology. 1997 Nov;26(5):1282-6.

The effects of hormone replacement therapy on ADPKD
We do have some data on the use of hormone replacement therapy. Again much of this comes from the Denver group. They administered estrogen therapy in the form of hormone replacement therapy in postmenopausal women for one year. They found that this increased in 11 women total liver volume by 7 percent versus in the eight individuals who did not take this, no change. The baseline symptoms of abdominal pain in 60 percent and shortness of breath in 40 percent were unaffected by the hormone replacement therapy, and there was no change in the size or the volume of the kidneys. We can talk more in detail about this in a few minutes, but the use of hormone replacement therapy really depends upon the individual and what their risk is for other estrogen deficiencies. That is are they at high risk for osteoporosis? Are they at high risk for heart disease? Are their postmenopausal symptoms disabling? And these are things that would need to be addressed before deciding whether or not to use hormone replacement therapy. It would also depend upon their extent of liver cyst disease.

00:00



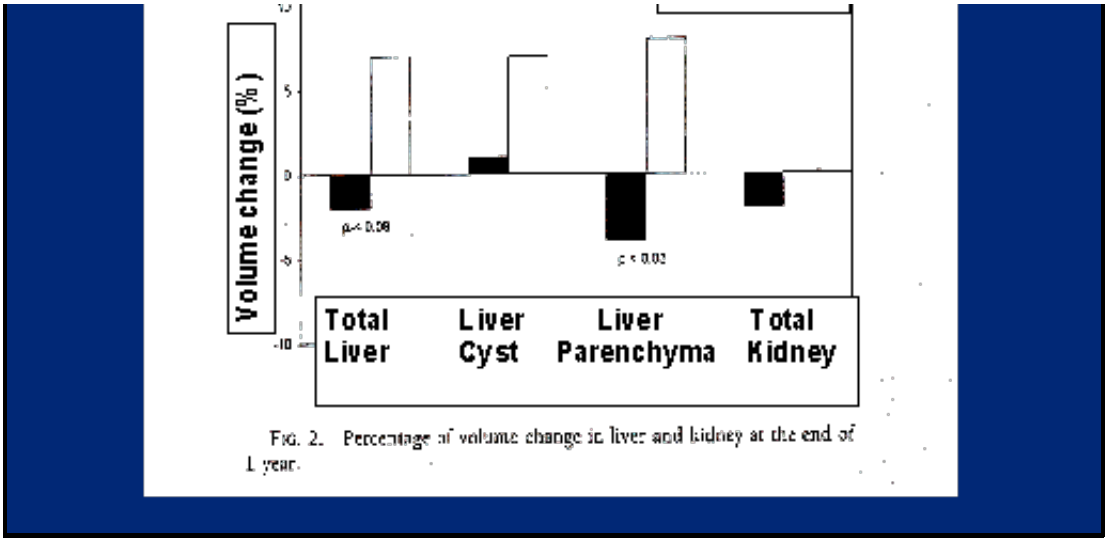
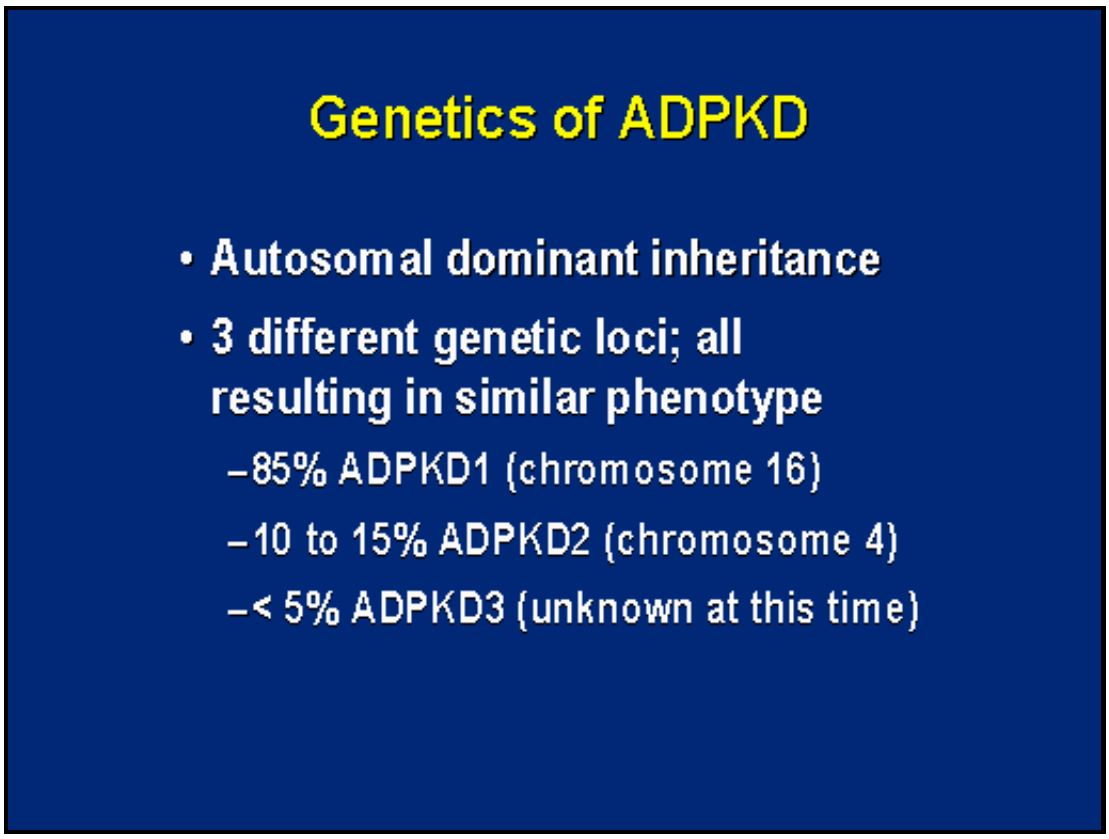


FIG. 2. Percentage of volume change in liver and kidney at the end of 1 year.

Source: Sherstha R et al, Hepatology. 1997 Nov;26(5):1282-6.

The effects of hormone replacement therapy on liver cysts
This is just a figure from the study that I just talked about. In the black squares are the control group. In the open squares are the estrogen. You can see that in the control group the liver cyst volume increased, no change in the kidney group in either one, and liver parenchyma also increased. So this one year of hormone therapy did seem to cause an increase in liver cyst volume in individuals who already had established liver cyst disease.

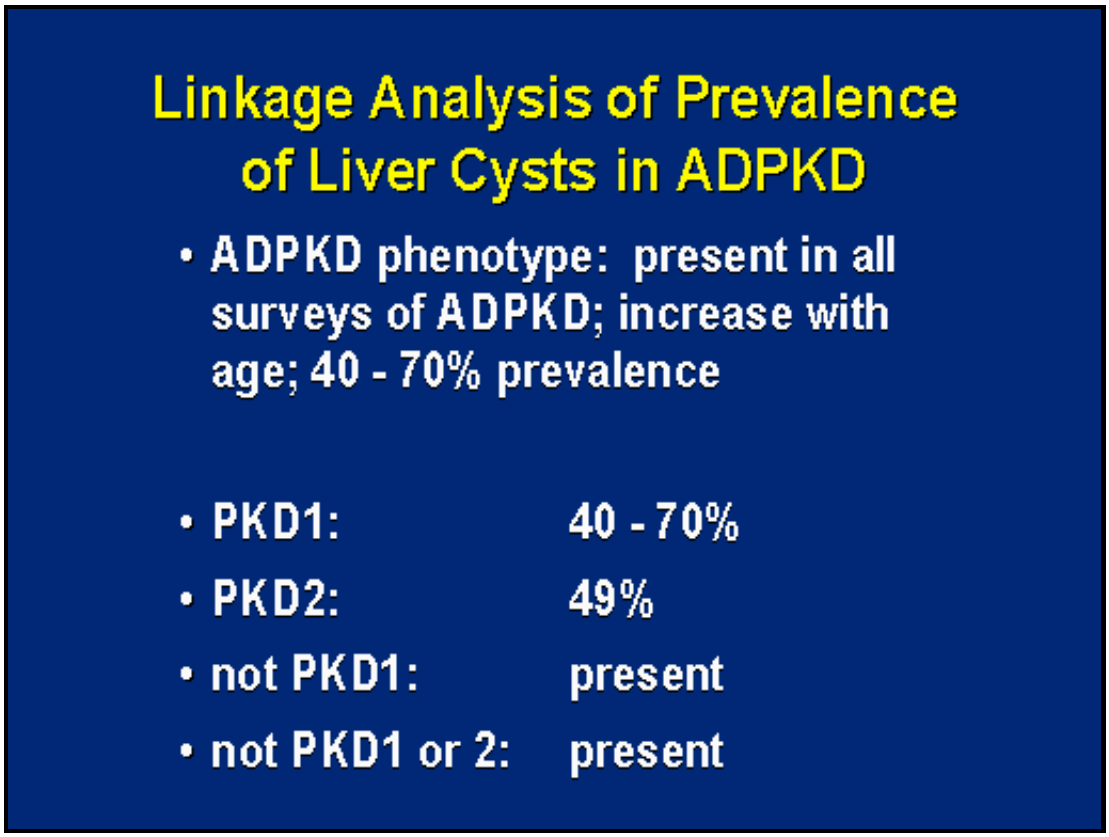
00:00



The genetics of ADPKD
A brief word about the genetics of PKD and the liver cyst disease within that context. We know that PKD is inherited in an autosomal dominant fashion, that is it is not on the sex chromosomes but on the other ones. We know that most individuals inherit the defect from a mutation of polycystin on chromosome 16, and a small number inherit the mutation from chromosome 4, and then a smaller number have a mutation that is presently undefined.

Whether this is one or multiple mutations is not known.

00:00

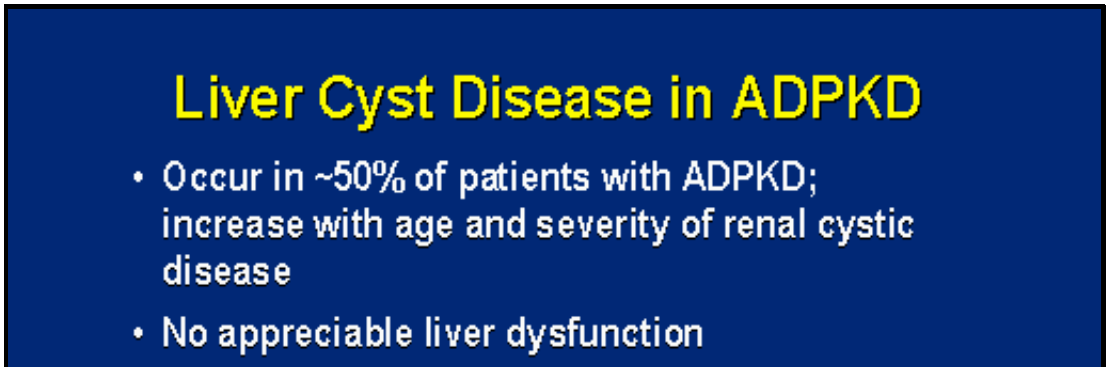


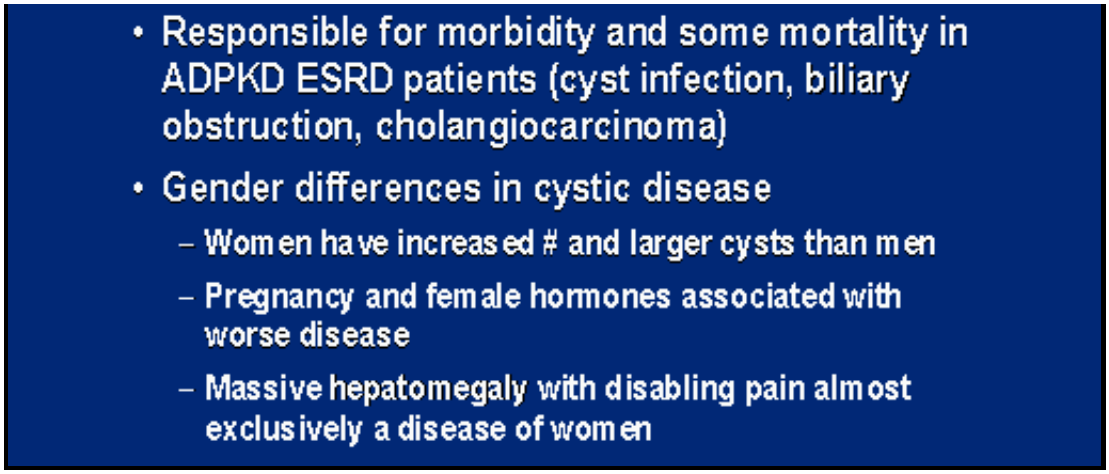
Do liver cysts occur in all types of genetic PKD?
What is known is that hepatic cysts, if you focus on the top row, are found in all forms of PKD. That is if you just randomly survey everyone with PKD without regard to their genetics, this 40 to 70 percent figure depends upon the age and whether their renal function has deteriorated. In PKD-1, linked to chromosome 16, again 40 to 70 percent; PKD-2, one study found 43 percent.

Recognize this is a cross-sectional study done at one point in time, so it is possible that this may be larger with age. In individuals who are not PKD-1, that means either the PKD-2 or the unknown or individuals who are unlinked to either -1 or -2, liver cysts are shown to be present. So as far as we know, liver cysts are part of all genetic forms of polycystic kidney disease.

What is not known, and I don't know if it will ever be known, is once the full range of mutations are described, will there be some mutations that have a greater association with liver cyst disease and others that don't? That is a question right now that we don't know the answer to.

00:00





Concluding remarks
In summary, I have gone over the general information about liver cysts in ADPKD. They occur in about 50 percent of individuals with PKD on average. These increase with age and with the severity of the renal cystic disease. They do not result in appreciable liver dysfunction. They are responsible for morbidity and some mortality in ADPKD patients with endstage renal disease, that is those who are on dialysis. The gender difference in cystic disease--women have an increased number and larger cysts than men. Pregnancy and female hormones are associated with worse disease. This massive polycystic liver disease with disabling pain is almost exclusively a disease of women.

Thank you for your attention. I could answer any questions now.

Discussion

Audience member: Could you say just one thing about the pancreatic cysts?

Dr. Perrone:
Cysts are reported in the pancreas in a small number of patients. Remember the pancreas is an organ that has two functions: It makes insulin and it is a digestive organ located adjacent to the small bowel. Most of the time, cysts in the pancreas are what we would call an incidental finding. That is they are there, they don't cause any symptoms, but certainly a cyst could enlarge that would cause problems. I think that happens very rarely.

Audience member:
A woman with PKD is placed on cholesterol medication. She has a cystic liver. Is she more at risk for having side effects with elevated liver enzymes?

Dr. Perrone:
One of the side effects of the statin-type medications is they cause an abnormality in the liver enzymes and even liver damage if the drug is not stopped. I am not aware of any data showing increased risk. I would suspect it is not increased because we suspect that the amount of functioning liver tissue is preserved. You have to be careful if people are taking cyclosporin or Prograf and the interactions among some of these medications, etc. The muscle enzymes are important.

Audience member:
Is there a relationship between declining kidney function and worse or larger liver cysts?

Dr. Perrone: Yes, there is a relationship. That is Little's cyst disease is worse in individuals with the poorest kidney function. We don't know why that occurs. Presumably there is something in the environment in an individual with kidney dysfunction that is somehow permitting the liver cysts to grow more actively, but we don't know what that is.

Audience member: Does transplant affect the liver cysts?

Dr. Perrone: Not that I am aware of. Again there are no data on that. So I don't really have the answer. I did an analysis of people on dialysis who had cause of death due to liver cysts and infections, and there were none that occurred after transplant. All of those that occurred did so prior to transplant. That doesn't necessarily mean that transplant is beneficial. It just means that those with more severe liver cyst disease didn't get transplanted and they stayed on dialysis. There was not any information about whether they were on hemo or PD.

Audience member:
I was wondering about stem cell transplantation. Is that recommended? Can that help in this particular problem?

Dr. Perrone:
There is no information yet on regeneration of whole organs with stem cell transplant and there is no information in PKD. I think it is an exciting area, but I think we have a long way to go.

Audience member:
A number of years ago, doctors used to drain cysts routinely. Is this still being done?

Dr. Perrone:
I hope I haven't conveyed the impression that we drain liver cysts routinely. We don't. We only do it for patients who are symptomatic from an enlarged cyst pressing on something. In fact, we would drain a kidney cyst if it were causing severe pain or a particular problem that wasn't resolved by other medications. In general you would only fenestrate or drain a liver cyst if it were causing significant pain or compression of another structure that was problematic.

Audience member:
You said as the kidneys got worse, the liver cysts got worse. Does it work the other way around?

Dr. Perrone:
Not necessarily. I know Dr. Torres has also has an experience of individuals with massive polycystic liver disease but with entirely normal kidney function. So that is certainly observed. These associations that are reported in these surveys and this does not reveal cause and effect, they just kind of reveal average relationships.

Audience member:
Is there a reason why the liver continues to function whereas the kidneys don't?

Dr. Perrone:
I am not aware of anyone actively doing research on that, but I think it is a very important area. My hunch is that there is this term... you might have heard about kidney cells, the term apoptosis? This programmed cell death that kidney cells seem to undergo. My hunch is that it doesn't happen in the liver, but that is just pure speculation. I think that would be a very interesting thing for somebody to look at.

Audience member:
In a previous meeting they said that after a kidney transplant the kidneys that are there go down in size. Does the same thing happen to liver at that point?

Dr. Perrone:
The native kidneys continue to deteriorate after a transplant; that is, more scarring takes place and blood flow goes down and certainly cyst formation can go down. I am not aware of any data looking at the liver cysts with regard to kidney transplant.

Audience member:
Are there any drugs available which would decrease the effect of secretin on liver cysts?

Dr. Perrone:

There are some medications that tend to reduce secretin--somatostatin is one of them. I believe metoclopramide is another one. I don't believe they have been shown to have any systematic effect in individuals with polycystic liver cysts.

Audience member:
Why do women get polycystic liver disease more than men? What does that tell us about how to prevent liver disease in both men and women if they don't have the disease yet?

Dr. Perrone:
The answer is not known. It is a fertile ground for investigation. But my hunch is it has something to do with ...the bile ducts or liver cells may have estrogen receptors that cause them to respond to these hormones. It raises the question of would tamoxifen or another one of these estrogen antagonists be helpful? Tamoxifen can be a fairly nasty drug, causing lots of complications, including blood clots. I am not aware of anyone who has studied it in polycystic liver disease. Again, you have the problem of both declining kidney function going along with the liver cyst disease. I think we need to know more about the basic function and the basic science of this before doing a clinical study. But I think it is a very important question.

Audience member:
When people have fatigue and declining blood counts, they develop anemia. At what point do you treat it?

Dr. Perrone:
There is a huge amount of attention now being paid to what we call pre-ESRD, pre-end-stage renal disease. With the availability of erythropoietin, clearly the ability to give this therapy is there. Generally a hematocrit of around 30 to 32 is the point where you need to start thinking about using these agents if people become symptomatic.

Then you get into a whole struggle with your insurance company. If you have Medicare, they won't pay for it because Medicare doesn't cover drugs. Depending upon who your private insurer is, typically the doctor has to write a letter or fill out some forms to jump through some hoops so you can get this drug paid for. If you have Medicaid, at least in Massachusetts, you can get erythropoietin paid for. It turns out that Blue Cross/Blue Shield is pretty liberal with giving erythropoietin, at least in the Boston area. Some of the other insurers are more difficult. But as long as the doctor writes the appropriate pre-approval letter saying that the kidney function is low, the GFR, and the individual needs erythropoietin to treat the anemia of kidney disease, we have found that no one will deny you if you jump through the hoops. You just have to make sure your doctor is willing to do that.

Audience member:
If you are taking estrogens and you have bad liver cyst disease, will stopping the estrogen or converting to a patch reverse the disease?

Dr. Perrone: Again there is no data. I would predict that there might be a slowing of the pace of the disease. But one of the things I didn't emphasize but what you see on any slide of a polycystic kidney or a liver is a tremendous amount of scar tissue. This scar tissue doesn't reverse when you stop the inciting event. So I suspect that there may be a slower rate of growth at best or perhaps stabilization. Unfortunately there aren't any magic bullets.

Audience member:
If you have part of the liver removed because of enlargement and painful liver cysts, can surgery be repeated in 5, 6, 10 years?

Dr. Perrone:
I don't know the answer to that because I don't think there are that many patients. Dr. Torres, who is at the meeting, probably could answer that question directly. I don't know if anyone has had a re-operation in his center. I think it would depend upon how much of the normal liver tissue was left. For example, if you had the operation where they removed one lobe of the liver and then it came back and they were able to remove another lobe of the

liver leaving you behind normal liver tissue, that would be certainly possible. But again it is big surgery, it is not without risk, and once you have done the surgery you develop scar tissue, adhesions, within the abdomen, which makes going back a second time more difficult. But that is not to say it couldn't be done. It would also depend upon what else is going on, whether the kidney function has deteriorated during that period of time. Those are complicated questions that are hard to answer just yes or no to. For example, it might be better the second time if kidney function has deteriorated to consider doing a transplant. But that is a very individualized decision.

Audience member:
If you have inherited polycystic kidney disease, what can you do to decrease the likelihood of liver cyst disease?

Dr. Perrone:
So how can you prevent the liver cysts from coming along? The only things we know about that we can control are estrogens. I think to make a decision whether or not to be pregnant and whether or not to ever use estrogens is a very individualized decision that someone would need to answer for themselves.

Audience member: But that doesn't affect men, obviously.

Dr. Perrone:
Right, neither the pregnancy nor the estrogens. I think that... for example, if I see a 20-year old woman who has just been diagnosed as having polycystic kidney disease, and frequently she would not have any liver cysts at that time, I would advise them of that. I would say, "Avoid unnecessary exposure to estrogens". They would be better off using barrier contraceptives for various reasons, not just that. It would also reduce the likelihood of sexually transmitted diseases. I would probably encourage them not to use oral contraceptives. Again, the decision about pregnancy is much more complicated than just the liver cysts. There is the genetic transmission, which is probably a far bigger issue that people have to suffer with when they think about that.

The other thing is caffeine. There is the experimental data in tissue culture showing that drugs that will increase the amount of cyclic AMP, and caffeine is one of those drugs that will at least theoretically do that. Eliminating caffeine might... again no data in humans... decrease the amount of secretion by cysts. My feeling is everything in moderation. I am not sure whether a cup of coffee a day versus no coffee a day is going to make a difference, but we don't know. Honestly, we really don't know.

Audience member: What effect does the massive liver have on survival?

Dr. Perrone: In the absence of an infection or a hemorrhage or some acute complication, the main effect of the massive liver is fatigue and poor nutrition. So if someone is on dialysis and they develop a large painful liver and have poor nutrition, then they are susceptible to more infections and more problems, and they lose weight, and they just deteriorate. And so that is the major concern in that individual. If you can keep up the nutrition despite that, which can be very hard because an individual gets filled up quickly and they don't like to eat-- that would be someone in whom I would consider doing the liver reduction surgery. If they couldn't eat and were dwindling in terms of losing weight and having severe pain and fatigue.

I will mention that I reviewed the entire dialysis experience from 1990 to about 1996-- 10,000 patients with PKD who were on dialysis. In twenty of those patients, their doctors indicated that liver cyst disease was one or one of several causes of death. So it is a small percentage when you look at it that way. Obviously it is a very big percentage for the individual involved. But it is not hundreds and hundreds and hundreds. It is small numbers.

Audience member:
Does severe liver cyst disease eliminate you from kidney transplant?

Dr. Perrone:

Just the large liver alone would not necessarily eliminate somebody. It depends upon the general state of health and how well they are doing. it is interesting that people who have tremendous trouble with liver cyst disease and massive livers can't get a liver transplant because they don't meet the conventional listing criteria for liver transplant, which are more based on liver function indices. So it is really very, very complicated. Now that the availability of living donor liver transplantation has come about, a family member can donate part of a liver now... so it is possible that some of these things may become treatable, just like kidney transplantation is widely used. So unless someone had really massive liver cyst disease that was really disabling and overwhelming, they would likely be a kidney transplant candidate.

I will stay up here and I would be happy to answer any individual questions.

References

1. Everson GT, Emmett M, Brown WR, Redmond P, Thickman D. Functional similarities of hepatic cystic and biliary epithelium: studies of fluid constituents and in vivo secretion in response to secretin. ***Hepatology. 1990 Apr;11(4):557-65.***

2. Baert L. Hereditary polycystic kidney disease (adult form): a microdissection study of two cases at an early stage of the disease. ***Kidney Int. 1978 Jun;13(6):519-25.***

3. Grimm PC, Crocker JF, Malatjalian DA, Ogborn MR. The microanatomy of the intrahepatic bile duct in polycystic disease: comparison of the cpk mouse and human. ***J Exp Pathol (Oxford). 1990 Feb;71(1):119-31.***

4. Perrone RD, Grubman SA, Rogers LC, Lee DW, Moy E, Murray SL, Torres VE, Jefferson DM. Continuous epithelial cell lines from ADPKD liver cysts exhibit characteristics of intrahepatic biliary epithelium. ***Am J Physiol. 1995 Sep;269(3 Pt 1):G335-45.***

5. Everson GT, Emmett M, Brown WR, Redmond P, Thickman D Functional similarities of hepatic cystic and biliary epithelium: studies of fluid constituents and in vivo secretion in response to secretin. ***Hepatology. 1990 Apr;11(4):557-65.***

6. Everson GT. Hepatic cysts in autosomal dominant polycystic kidney disease. ***Am J Kidney Dis. 1993 Oct;22(4):520-5. No abstract available.***

7. Sherstha R, McKinley C, Russ P, Scherzinger A, Bronner T, Showalter R, Everson GT. Postmenopausal estrogen therapy selectively stimulates hepatic enlargement in women with autosomal dominant polycystic kidney disease. ***Hepatology. 1997 Nov;26(5):1282-6.***

Back to Topic Index: Return to Home Page

Topic Index: **Clinical Nephrology -- Polycystic Kidney Disease**

Back to list of talks for this symposium
Back to symposia list by topic
Back to symposia list by meeting
Back to HDCN home page