undetectable by computed tomography (CT) scan. We are not given this information in the first study, but benign regenerative nodules are typically not visible by CT. If a focal lesion is confirmed by CT scan, again the question of malignancy should be raised. (d) Most lesions in the first study but not the second study enlarged with follow-up, which should also suggest HCC.

So what should we do with the asymptomatic patient with known cirrhosis and a focal lesion demonstrated by ultrasound? Most are going to have HCC. If the α-fetoprotein (AFP) level is high (>1,000 ng/ml), the patient almost certainly has HCC, and histological confirmation may not be necessary. A low AFP does not rule out malignancy. Although CT scan is not feasible for screening programs in the Far East, in the United States most ultrasound lesions will be confirmed by CT before obtaining the histological study. Ultrasound-guided, FNA should then be performed and, if histologically benign, repeated with a thin liver-biopsy needle. If the diagnosis of HCC is not made, the prudent course is to observe the patient. A rising AFP level and/or sonographic enlargement of the lesion should prompt further invasive evaluation by either an ultrasound-guided or laparoscopic biopsy procedure.

Are regenerative nodules premalignant lesions? The cirrhotic liver *per se* is associated with an increased risk of HCC, the risk varying with the cause of the liver disease. However, regenerative nodule is not synonymous with focal liver lesion. Every focal mass lesion in a cirrhotic liver should simply be considered malignant until proven otherwise (e.g., with a follow-up of more than 2 yr without observed progression). With careful evaluation, most will be shown to be malignant initially. The evidence that large regenerative nodules have greater malignant potential than the surrounding cirrhotic liver is slim at best.

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## LIVER TRANSPLANTATION RESTORES FEMALE REPRODUCTIVE ENDOCRINE FUNCTION

*Cundy TF, O'Grady JG, Williams R.* Recovery of menstruation and pregnancy after liver transplantation. Gut 1990;31:337-338.

### ABSTRACT

**The effect of successful liver transplantation on menstrual function was assessed by questionnaire in 44 women transplanted for various types of end stage liver disease, acute liver failure or malignant disease. Significant amenorrhoea (>one year) was present in 48% of women with chronic liver disease before transplantation, and was reversed within 10 months of surgery in all but one of the pre-menopausal patients who had primary amenorrhoea and hypogonadotrophic hypogonadism. Two patients became pregnant five months and 1-5 years after transplantation, but in one instance the pregnancy was unsuccessful, possibly as a consequence of cyclosporin related intrauterine growth retardation.**

*Scantlebury V, Gordon R, Tzakis A, Koneru B, Bowman J, Mazzaferro V, Stevenson WC, et al.* Childbearing after liver transplantation. Transplantation 1990;49: 317-321.

### ABSTRACT

**Seventeen female patients who underwent orthotopic liver transplantation between June 1973 and June 1987 became pregnant 5 months to 11 years after transplantation. Immunosuppression was maintained with combinations of prednisone, cyclosporine, and azathioprine prior to and during pregnancy. One patient discontinued immunosuppression after knowledge of pregnancy, taking only azathioprine sporadically. Mean age at time of delivery was 26 years. Twelve patients had no alteration in liver function studies; 7 patients demonstrated mild or moderate enzyme elevations prior to delivery, with one case of rejection confirmed by percutaneous liver biopsy. Major problems related to pregnancy were hypertension, anemia, and hyperbilirubinemia. Twenty live births occurred (2 patients had 2 separate pregnancies, one patient has a set of twins); 13 were by caesarian section, 7 by vaginal delivery. Eleven of the 13 caesarian births were premature by gestational age. All vaginal births were term. Toxemia of pregnancy and early rupture of membranes were the principal indications for caesarean section.**

**There were no congenital abnormalities or birth defects and all the children are surviving well. Fifteen of 16 children older than one year have normal physical and mental development, with one child manifesting immature speech development. Four children are under one year, all with normal milestones thus far. Sixteen of the 17 mothers are alive from 2-18 years after transplantation; the only death was from a lymphoma, almost 4 years after transplantation and 2½ years after delivery. This experience suggests that women undergoing liver transplantation can safely bear children despite an increased risk of premature caesarian births. The effect of chronic immunosuppression of female pediatric patients on their reproductive potential later in adulthood remains to be fully evaluated but the results so far are favorable.**

### COMMENTS

In the past 20 yr, liver transplantation has emerged as the treatment of choice for many symptomatic patients

with acute and chronic liver disease. Now that an 80% 1-yr survival rate is commonplace, and long-term survival beyond this is expected in many liver transplant recipients, patients and physicians have begun to look beyond quantity of life to quality of life after transplantation. The endocrine and tissue abnormalities underlying sexual dysfunction in cirrhosis are complex, and their potential for reversal with liver transplantation are important issues in determining restoration of normal sexual and reproductive function. The two articles under review provide valuable information for female patients who are undergoing liver transplantation evaluation when they inquire whether menstruation, conception and pregnancy are possible after liver transplantation.

To date, most work describing changes in the hypothalamic-pituitary-gonadal axis in patients with chronic liver disease has focused on alcoholic patients. It has been suggested that alcohol rather than the chronic liver disease itself may account for many of the changes seen in these patients (1). Men with alcoholic liver disease exhibit testicular atrophy, impotence and decreased libido. It has been suggested that a change in the redox state in the testes or the accumulation of acetaldehyde may interfere with steroidogenesis or have a direct toxic effect on the cells (1). Interference with normal metabolism of vitamin A (necessary for spermatogenesis) may also play a role (1). Similarly, women with alcoholic liver disease exhibit ovulatory failure, reduced estradiol and progesterone levels and loss of secondary sexual characteristics. The biochemical mechanism may be similar to that seen in alcoholic men (1). In addition, alcoholic men and women both show evidence of a central hypothalamic-pituitary defect in gonadotropin secretion (1). In contrast, men with presumed chronic viral liver disease have normal levels of testosterone and maintain an appropriate luteinizing-hormone (LH) response to the LH releasing factor when compared with alcoholic men (2). Studies of women with nonalcoholic liver disease have not been conducted to the same extent. However, hypothalamic-pituitary-gonadal function in women with nonalcoholic forms of cirrhosis is frequently abnormal, as shown by the incidence of prolonged amenorrhea in female cirrhotic patients before liver transplantation as reported by Cundy, O'Grady and Williams.

Few reports discuss the effect of liver transplantation on the hypothalamic-pituitary-gonadal function. Recently, Van Thiel et al. (3) evaluated these issues in alcoholic and nonalcoholic men undergoing transplantation. Compared with nonalcoholic men, alcoholic men exhibited decreased plasma levels of testosterone, follicle-stimulating hormone (FSH) and LH before transplantation. Additionally, they reported a greater frequency and severity of impotence. After successful liver transplantation, plasma levels of FSH, LH and testosterone returned toward normal levels, and these hormonal changes were accompanied by a reduction in the frequency and severity of impotence in the alcoholic men. They suggest that liver transplantation in alcoholic cirrhotic men improves the functioning of the hypothalamic-pituitary-gonadal axis considerably but does not return it to complete normalcy (3).

Heretofore, data concerning reproductive endocrine function in female liver transplant recipients consisted of case reports describing pregnancy and parenthood after liver transplantation (4). The papers by Cundy, O'Grady and Williams and Scantlebury et al. are the first collective descriptions of menstrual patterns and pregnancy in women after liver transplantation. Cundy and colleagues specifically address the question of recovery of menstruation after liver transplantation. Of 34 patients, 28 resumed menstruation within 10 mo of transplantation, and 5 patients appeared to be postmenopausal because of age and elevation of FSH and LH. Most interesting was the observation that menstruation returned within 2 mo after transplantation in 41% of the patients and by 5 mo in 79% of the patients. This suggests the underlying defect is corrected quickly and that one needs to counsel patients concerning the need for contraception as soon as sexual activity is resumed if pregnancy is not desired.

The outcome of pregnancy when it does occur after transplantation seems to be fairly good. Scantlebury et al. describe 17 patients who became pregnant after liver transplantation and explain several important points. First, graft function appeared to be maintained throughout pregnancy and delivery. Thirty-five percent of pregnant patients had a rise in transaminase levels, but only one episode of acute rejection was documented. After delivery, 10 of 17 patients had elevated enzymes. Four patients were treated empirically for rejection with only one of four responding, suggesting that of these patients, even in this low incidence, rejection may have been overdiagnosed. Because of the confounding incidence of hypertension and toxemia in this series, it is difficult to interpret these moderate biochemical changes. First, it is known that up to 60% of patients with toxemia of pregnancy may exhibit moderate transaminase elevations (5). Second, the major maternal complications seen were hypertension and anemia. It is likely that cyclosporine contributed to the high incidence of hypertension and toxemia in these patients. Sixty-three percent of the patients had deliveries by cesarean section, a rate much higher than the 24% rate usual in the United States (6). Nonetheless, no maternal deaths were reported. Third, despite continued immunosuppression in 16 of 17 patients, infants born to these mothers generally did well. Overall, only one infant required mechanical ventilation. No infections or other complications were seen. Although fears exist that prednisone or azathioprine may have teratogenic consequences, the lack of congenital abnormalities observed in this series is in accord with observations on the use of these agents in pregnant renal transplant recipients or patients with inflammatory bowel disease (7). Cyclosporine crosses the placenta readily (Bourget, et al. Transplantation 1990;49:663-664, Correspondence) but has not been shown to produce congenital abnormalities.

The possibility that it may result in intrauterine growth retardation has been suggested (8, 9), and that was seen in three patients in the Scantlebury et al. series and one patient reported by Cundy, O'Grady and Williams. The importance of this is unclear, given that intrauterine growth retardation can be seen in up to 10% of ostensibly normal pregnancies.

The single case reported in the Scantlebury et al. article of a patient who stopped all medication in pregnancy is fascinating. Pregnancy is a state of altered immunity allowing retention of a foreign tissue mass (the fetus). The low incidence of allograft rejection reported by Scantlebury et al. and the successful withdrawal of immunosuppressive agents, albeit in one recipient only, imply that lower doses of immunosuppressive agents may be effective during pregnancy.

It appears from these articles that (a) menstruation returns in concert with restored hepatic function, and (b) pregnancy is possible and relatively safe after liver transplantation. Indeed, liver transplantation can sustain the life of mother and fetus even in the extreme circumstances of decompensated liver failure during pregnancy (10). All in all, these articles contain reassuring news for young women facing the ordeal of liver transplantation.

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## URSODEOXYCHOLIC ACID AND TAURINE AS THERAPY FOR CHOLESTATIC LIVER DISEASE

*Podda M, Ghezzi C, Battezzati PM, Crosignani A, Zuin M, Roda A.* Effects of ursodeoxycholic acid and taurine on serum liver enzymes and bile acids in chronic hepatitis. Gastroenterology 1990;98:1044-1050.

### ABSTRACT

**Relatively hydrophobic bile acids have been shown to produce some hepatotoxicity, whereas treatment with a more hydrophilic bile acid, ursodeoxycholic acid, has improved liver function indices in patients with certain chronic liver diseases. Taurine-conjugated bile acids are more hydrophilic than glycine-conjugated bile acids, and thus, taurine administration has also been suggested for the treatment of chronic hepatitis. To determine if taurine and ursodeoxycholic acid are beneficial and if their effects are additive, this double-blind, randomized trial was conducted to compare the effects of ursodeoxycholic acid, taurine, and a combination of the two on indices of liver injury in 24 patients with chronic hepatitis.**

**The subjects were assigned at random to two of the four following treatments: ursodeoxycholic acid (600 mg/d), taurine (1.5 g/d), ursodeoxycholic acid plus taurine (600 mg and 1.5 g/d) or placebo, given in two successive cycles of 2 months each, according to a balanced incomplete block design.**

**As expected, ursodeoxycholic acid became the predominant bile acid in bile when administered alone or in combination with taurine, and taurine conjugate concentrations increased during taurine administration. Ursodeoxycholic acid reduced serum aminotransaminase and γ-glutamyl transpeptidase activities significantly, whereas taurine did not. The effects of taurine and ursodeoxycholic acid were not significantly different from those produced by ursodeoxycholic acid alone. It is concluded that ursodeoxycholic acid, but not taurine, improves biochemical indices of liver injury in patients with chronic hepatitis.**

### COMMENTS

Ursodeoxycholic acid (UDCA) has been reported to improve pruritus and biochemical profiles of patients with cholestatic liver diseases such as PBC. Several hypotheses have been proposed to explain these results, with reports based on what is known about bile acid (BA) metabolism, physiology and the enterohepatic circulation, but the exact mechanism(s) of these beneficial effects is not known.

Chenodeoxycholic acid (CDCA) and lithocholic acid appear to be more toxic than more hydrophilic BAs. Hydrophilicity *in vivo* is achieved by hydroxylation and/or conjugation, including glucuronidation, sulfation and amidation with glycine or taurine.

Taurine-conjugated BAs are more hydrophilic than glycine conjugates, but glycine conjugates predominate under normal circumstances. Previous studies have shown that feeding taurine to normal humans causes the reversal of the glycine/taurine conjugation ratio (1).

UDCA is the 7β-epimer of CDCA. The 7β-hydroxyl