



Estrogens and Oral Contraceptives

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OVERVIEW

Introduction

Estrogens and oral contraceptives are both associated with several liver related complications including intrahepatic cholestasis, sinusoidal dilatation, peliosis hepatis, hepatic adenomas, hepatocellular carcinoma, hepatic venous thrombosis and an increased risk of gallstones. These side effects are more common with higher doses of estrogens, as were used in the early high dose estrogen formulation of oral contraceptives, but they have also been described with use of more modern birth control pills and with low dose, estrogen hormonal replacement therapy.

Background

Synthetic estrogens for regulation of menstrual cycles and hormonal replacement therapy were developed in the early 1950s and came into increasing use in thereafter. Oral contraceptives (OCCs) were approved for use in the United States in 1960 and became widely used. Initial OCCs (first generation) used somewhat high doses of estrogens (50 µg of mestranol or 20 to 50 µg of ethinyl estradiol) in combination with a progestin and had appreciable rates of estrogenic side effects. Second and third generation OCCs introduced in the 1980s and 1990s have lower doses of ethinyl estradiol (15 to 35 µg) and more modern forms of progestins (norgestrel, desogestrel and others), which have been associated with lower rates of estrogenic and other adverse side effects. Hormonal replacement therapy became increasing popular in the 1980s and 1990s. Both estrogen only and combination forms of hormonal replacement therapy were used. In women with a uterus, combination hormonal replacement therapy was recommended usually combining a conjugated equine estrogen with medroxyprogesterone. The estrogen doses used in hormonal replacement therapy were 5 to 6 times lower than the equivalent ethinylestradiol doses used in OCCs. The popularity of hormonal replacement therapy decreased in the late 1990s when prospective studies demonstrated excess morbidity and mortality associated with replacement therapy in postmenopausal women. Commercially available OCCs include monophasic, biphasic, triphasic, extended cycle and progestin only formulations. Hormonal replacement therapy usually employs conjugated equine estrogen in doses of 1.25 mg per day, with medroxyprogesterone late in the menstrual cycle.

Hepatotoxicity

While early formulations of OCCs were associated with frequent serum enzyme elevations, current formulations and hormonal replacement therapy have not been linked to ALT or alkaline phosphatase elevations at rates any higher than occur with placebo. Estrogens and OCCs can cause mild inhibition of bilirubin excretion, leading to jaundice in patients with inherited forms of bilirubin metabolism such as the Dubin Johnson syndrome. More importantly, estrogens and OCCs can induce a clinically apparent cholestatic liver injury which typically arises

during the first few cycles of therapy, and rarely after the six months (Case 1). The onset is typically insidious with fatigue and pruritus, followed by nausea, dark urine and jaundice. Serum enzyme elevations are usually mixed or cholestatic, although very early during the injury, ALT levels can be markedly elevated (5- to 20-fold). The characteristic pattern, however, is bland intrahepatic cholestasis and liver biopsy shows little inflammation or hepatocyte necrosis. Resolution may be delayed (Case 2), but estrogens have not been definitely linked to chronic injury, vanishing bile duct syndrome or acute liver failure. Women with OCC induced cholestasis often have a history of idiopathic cholestasis of pregnancy and there is likely a genetic component, most commonly with variants in the bile salt export pump (BSEP, ABC B11). Estrogens and particularly combinations of estrogens and progestins have been linked to episodes of marked serum aminotransferase elevations without symptoms, jaundice or cholestasis. The abnormalities resolve quickly with stopping the hormonal treatment. This syndrome may be more frequent with progestins than with estrogens alone.

Estrogens and OCCs have also been linked to hepatic tumors, both benign and malignant. Numerous reports of hepatic adenomas have been linked to estrogen and OCC use, typically arising after several years of use and presenting either with pain, liver mass or rupture with hemoperitoneum (Case 3). In population based surveys, the risk of developing hepatic adenomas on OCCs is estimated to be 0.5% per year. In some instances, malignant transformation and hepatocellular carcinoma have been found. Benign tumors may regress to some extent with stopping estrogens, but others require intervention. Estrogens may also promote the growth of other benign liver tumors, such as focal nodular hyperplasia, hemangiomas, and hamartomas.

Hepatocellular carcinoma has been linked to use of oral contraceptives in several case reports and case controlled studies. However, in larger studies and population based analyses, oral contraceptives have not been clearly linked to liver cancer. Hepatocellular carcinoma is extremely rare in young women without accompanying liver disease, and even if oral contraceptives increase the risk of this cancer by 2- to 3-fold, it remains extremely rare.

Use of oral contraceptives has also been linked to an increase in venous thrombosis and cases of hepatic venous thrombosis or Budd Chiari syndrome (Case 4). Women who develop this complication are often found to have other risk factors for venous thromboses such as Protein C or Protein S deficiency or Factor V Leiden. Portal vein thrombosis has also been reported with oral contraceptive use.

Chronic use of oral contraceptives is associated with sinusoidal dilatation, a finding on liver biopsy of uncertain significance. Extreme sinusoidal dilatation associated with venous lakes and propensity for hepatic rupture is referred to as peliosis hepatis, which can be associated with symptoms and hepatic rupture. Oral contraceptive use has been associated with rare instances of peliosis hepatis, but the association a striking dilation of sinusoids with venous lakes has been rarely reported with oral contraceptive use. Stopping oral contraceptives has occasionally been associated with regression in the severity of peliosis.

Both oral contraceptives and chronic hormonal replacement therapy are also associated with a slight increased rate of gallbladder disease, typically occurring during the first few years of estrogen use.

Likelihood score: A (well known cause of various forms of clinically apparent liver injury).

Mechanism of Injury

Cholestasis due to estrogens and OCCs appears to be related to inhibition of bilirubin and bile acid secretion related to effects of estrogens on the orphan nuclear receptors that modulate bile acid and bilirubin metabolism. Women with cholestasis caused by OCCs often have a history of cholestasis of pregnancy (with jaundice and/or pruritus), and genetic variations in bile acid transporter genes (ABC B4, B11 and C2) are frequent. In addition, women who develop hepatic adenomas on OCCs are often heterozygous for gene variations associated with multiple hepatic adenomas such as in hepatic nuclear factor 1 alpha (HNF1-alpha).

Outcome and Management

The cholestasis associated with OCCs is typically mild and resolves rapidly with stopping. Some cases, however, are protracted and associated with severe pruritus with or without marked jaundice. The efficacy of ursodiol in treating the cholestasis of pregnancy makes this approach appropriate in women who develop cholestasis due to OCCs in whom symptoms are problematic; the dosage is 12 to 15 mg/kg/day and it should be continued until symptoms and major blood test abnormalities have resolved. Corticosteroids should not be used. Recurrence of cholestasis with restarting OCCs is typical, although lower dose formulations may be found that do not trigger the response. Management of hepatic tumors related to OCCs is complex. In many instances, merely stopping oral contraceptives is followed by regression in the tumor size, but surgery may be required for larger tumors and those in which malignant transformation is believed to a risk.

See also [Progesterone and the Progestins](#)

CASE REPORTS

Case 1. Cholestasis due to birth control pills.(1)

A 28 year old woman developed pruritus within 4 days of starting oral contraceptives and stopped them after a week. One week later (14 days after starting), she had darkening of the urine and 4 weeks later was found to be jaundiced. She was taking no other medications and had no risk factors for viral hepatitis. Important in her past medical history were episodes of jaundice and pruritus during two pregnancies. The jaundice arose during the fifth month of her second and the sixth week of her third pregnancies with peak bilirubin values of 3.5 and 3.8 mg/dL and prominence of pruritus. The cause of jaundice during her pregnancies was not identified despite extensive evaluation including laparotomy and cholecystectomy (the gallbladder was normal without stones). Thereafter, she was well until she started birth control pills. On examination, she was jaundiced but had no fever or rash. Serum bilirubin was 4.5 mg/dL, ALT 352 U/L and alkaline phosphatase 24 King Armstrong units (~2 times upper limit of normal) (Table). A liver biopsy showed intrahepatic cholestasis with minimal inflammation. Upon stopping the contraceptive pills, serum laboratory tests improved and jaundice cleared within 2 weeks. However, she continued to have pruritus for 3 months after stopping the medication. Ultimately, all symptoms and itching resolved and laboratory tests except for alkaline phosphatase were normal 6 months later.

Key Points

| | |
|--------------------|--|
| Medication: | Enovid (once daily) |
| Pattern: | Mixed (R=4.9) |
| Severity: | 3+ (jaundice, hospitalization) |
| Latency: | 4 days to symptoms, 2 weeks to jaundice |
| Recovery: | Jaundice resolved in 2 weeks, symptoms in 3 months |
| Other medications: | None |

Laboratory Values

| Time After Starting | Time After Stopping | ALT (U/L) | Alk P (KA U/L) | Bilirubin (mg/dL) | Other |
|------------------------------|---------------------|-----------|----------------|-------------------|----------------------|
| Enovid once daily for 7 days | | | | | |
| 6 weeks | 5 weeks | 352 | 24 | 4.2 | Direct bilirubin 2.4 |
| 7 weeks | 6 weeks | 356 | 25 | 5.5 | Liver biopsy |
| 3 months | 11 weeks | 58 | 27 | 1.2 | |

Table continued from previous page.

| Time After Starting | Time After Stopping | ALT (U/L) | Alk P (KA U/L) | Bilirubin (mg/dL) | Other |
|----------------------|---------------------|---------------|----------------|-------------------|-------|
| 8 months | 30 weeks | 38 | 20 | 0.8 | |
| Normal Values | | <40 | <13 | <1.2 | |

Comment

A woman with a history of idiopathic cholestasis of pregnancy developed pruritus a few days after starting birth control pills, and dark urine followed by jaundice several weeks later. The ratio of ALT to alkaline phosphatase elevations suggested that the injury was "mixed," but the liver biopsy showed bland intrahepatic cholestasis with little hepatocyte necrosis or inflammation, and the symptoms were decidedly cholestatic with a prominence of pruritus that only slowly resolved.

Case 2. Prolonged cholestasis due to birth control pills.(2)

A 22 year old woman developed jaundice and pruritus after a single 28 day cycle of oral contraceptives (L-Ovral: orgestrel 0.3 mg and ethinyl estradiol 0.03 mg) which were started shortly after a first trimester abortion. Over the next several months, she developed worsening pruritus, anorexia, nausea, fatigue and weight loss. She had no previous history of liver disease or risk factors for viral hepatitis. Her only medications were birth control pills and rarely acetaminophen for pain. Examination showed marked jaundice and multiple excoriations. The liver was enlarged and somewhat tender to palpation. Laboratory results showed bilirubin of 7.0 mg/dL, ALT 80 U/L and Alk P 170 U/L (Table). Because of persistent jaundice, she underwent endoscopic retrograde cholangiopancreatography which was normal. A liver biopsy showed intrahepatic cholestasis with minimal inflammation and bile duct proliferation. She eventually began to improve and all laboratory values were normal or near normal 6 months later.

Key Points

| | |
|--------------------|------------------------------------|
| Medication: | L-Ovral (once daily for one cycle) |
| Pattern: | Cholestatic (R=1.7 falling to 0.9) |
| Severity: | 3+ (jaundice, prolonged) |
| Latency: | 1 month |
| Recovery: | 6 months |
| Other medications: | Occasional acetaminophen |

Laboratory Values

| Time After Starting | Time After Stopping | AST* (U/L) | Alk P* (U/L) | Bilirubin* (mg/dL) | Other |
|--------------------------------|---------------------|------------|--------------|--------------------|-----------------------|
| L-Ovral once daily for 28 days | | | | | |
| 1 month | 0 | 90 | 165 | 7.0 | Pruritus and jaundice |
| | 2 weeks | 80 | 250 | 11.0 | |
| 2 months | 4 weeks | 105 | 290 | 15.3 | |
| | 6 weeks | 110 | 405 | 17.5 | ERCP and liver biopsy |
| 3 months | 8 weeks | 130 | 380 | 18.2 | |
| | 10 weeks | 145 | 390 | 19.5 | |

Table continued from previous page.

| Time After Starting | Time After Stopping | AST* (U/L) | Alk P* (U/L) | Bilirubin* (mg/dL) | Other |
|----------------------|---------------------|---------------|----------------|--------------------|-------|
| 4 months | 12 weeks | 155 | 490 | 17.5 | |
| | 14 weeks | 190 | 556 | 13.6 | |
| 5 months | 4 months | 219 | 360 | 5.8 | |
| 6 months | 5 months | 60 | 200 | 1.7 | |
| 7 months | 6 months | 35 | 125 | 0.5 | |
| Normal Values | | <40 | <115 | <1.2 | |

* Values and dates estimated from Figure 1.

Comment

Oral contraceptive induced jaundice usually arises during the first cycle of birth control pills and is typically cholestatic with mild jaundice and pruritus, resolving in 1 to 2 months. In this instance, jaundice and pruritus were prolonged and laboratory values did not return to normal or near normal for 6 months. While oral contraceptives can cause prolonged jaundice, they have not been definitely associated with vanishing bile duct syndrome or fatal liver disease.

Case 3. Hepatic adenoma due to birth control pills.(3)

A 28 year old woman who had been on oral contraceptives (0.25 mg d-norgestrel and 0.05 mg ethinyl estradiol: Ovral) for 7 years presented with dull, but steady right upper quadrant pain lasting for two days. She had no other significant medical problems and took no medications except occasional aspirin. She rarely drank alcohol and had no risk factors for viral hepatitis or liver disease. Physical examination revealed an obvious mass in the epigastrium and right upper quadrant that appeared to involve the liver. There was no tenderness, ascites, wasting or jaundice. Laboratory results showed an alkaline phosphatase of 1038 U/L, but normal bilirubin and ALT. The sedimentation rate was 59 mm/hr and hemoglobin 10.4 g/dL. A technetium colloid liver-spleen scan showed a large liver, but no obvious masses whereas a HIDA scan showed a large hypofunctioning mass in the liver. A liver biopsy showed hepatic adenoma with sinusoidal dilatation. A hepatic arteriogram showed a large vascular tumor occupying most of the right and central lobes. Resection was not considered technically possible. Oral contraceptives were stopped and she underwent tubal ligation. During the ensuing 12 months she remained well and repeat scans showed return of liver to normal size. Alkaline phosphatase also fell to normal.

Key Points

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|--------------------|--|
| Medication: | Oral contraceptives for 7 years |
| Pattern: | Alkaline phosphatase elevation only |
| Latency: | 7 years |
| Recovery: | Radiological resolution over 12 months |
| Other medications: | Aspirin |

Comment

Hepatic adenomas are a rare, but well defined complication of long term use of oral contraceptives. They can present in three manners: (1) with sudden acute right upper quadrant pain and rupture, (2) as an abdominal mass with or without mild degrees of pain, or (3) as an incidental finding on physical examination, during unrelated abdominal surgery or on routine radiological imaging. The association of contraceptive use and hepatic adenomas has been made both epidemiologically and clinically, the clinical evidence being supported by

the rarity of this tumor before the introduction of oral contraceptives, and the spontaneous resolution or shrinkage of the tumors upon withdrawal of the pill as in this case. Serum alkaline phosphatase levels are raised in some, but certainly not all women with this tumor and liver tests are typically normal. In this instance, the high alkaline phosphatase levels were probably related to the size of the tumor and its encroachment on the normal liver and biliary system. This case also demonstrates that the tumor can be managed by stopping the oral contraceptives and careful follow up. In rare instances, hepatic adenomas have later been found to show malignant transformation. There is likely a genetic basis to the development of hepatic adenomas on oral contraceptives.

Case 4. Budd Chiari syndrome in a woman on long term oral contraceptives.(4)

A 26 year old woman presented with a three month history of abdominal and lower leg swelling associated with a 30 pound weight gain. She was on oral contraceptives which she had taken on and off for a total of 7 years. She denied history of liver disease, abdominal trauma or previous problems with venous thrombosis. Examination showed severe ascites and peripheral edema without jaundice or peripheral manifestations of chronic liver disease. She did not drink alcohol and had no history of high risk behaviors. Laboratory testing showed a normal bilirubin [0.6 mg/dL] and ALT [10 U/L] with mild elevations in alkaline phosphatase [189 U/L]. Hepatic imaging showed enlargement of the caudate lobe and evidence of hepatic venous thrombosis. Oral contraceptives were stopped and she was treated with salt restriction, diuretics, aspirin and dipyridamole. Over the next few weeks, her ascites and fluid retention resolved. She did not have recurrence of abdominal pain or ascites during a follow up period of 22 months.

Key Points

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|-------------|---|
| Medication: | Ovulen 21 (two years, previously 5 years) |
|-------------|---|

Comment

A woman developed hepatic vein thrombosis (Budd Chiari syndrome) with a subacute presentation of fluid retention and ascites during long term oral contraceptive use. No other predisposing factors for venous thrombosis was identified, but this syndrome most frequently occurs in persons with an underlying hypercoagulable state such as a myeloproliferative disorder or acquired abnormalities of coagulation such as the lupus anticoagulant or anticardiolipin antibodies, or inherited abnormalities such as in protein C and S or abnormalities of clotting factors V and II. Thus, Budd Chiari syndrome occurring in women on oral contraceptives may represent a paradigm of drug induced liver injury, resulting from the combination of an environmental exposure (oral contraceptives) and host, genetic predisposition.

PRODUCT INFORMATION

DRUG CLASS

Hormones and Synthetic Substitutes:

Contraceptives, Oral; Estrogens

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CITED REFERENCES

1. Boake WC, Schade SG, Morrissey JF, Schaffner F. Intrahepatic cholestatic jaundice of pregnancy followed by Enovid-induced cholestatic jaundice. *Ann Intern Med.* 1965;63:302–8. PubMed PMID: 14318470.
2. Lieberman DA, Keefe LB, Stenzel P. Severe and prolonged oral contraceptive jaundice. *J Clin Gastroenterol.* 1984;6:145–8. PubMed PMID: 6715853.
3. Steinbrecher UP, Lisbona R, Huang SN, Mishkin SI. Complete regression of hepatocellular adenoma after withdrawal of oral contraceptive use. *Dig Dis Sci.* 1981;26:1045–50. PubMed PMID: 6271517.
4. Lewis JH, Tice HL, Zimmerman HJ. Budd-Chiari syndrome associated with oral contraceptive steroids: review of treatment of 47 cases. *Dig Dis Sci.* 1983;28:673–83. PubMed PMID: 6872799.

ANNOTATED BIBLIOGRAPHY

References updated: 30 May 2020

Abbreviations: OCC, oral contraceptives; FNH, focal nodular hyperplasia; BRIC, benign recurrent intrahepatic cholestasis.

Zimmerman HJ. Hormonal derivatives and related drugs. In, Zimmerman HJ. *Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver.* 2nd ed. Philadelphia: Lippincott, 1999, pp. 555-88.

(Expert review of effects of estrogens and birth control pills on the liver).

Chitturi S, Farrell GC. Adverse effects of hormones and hormone antagonists on the liver. In, Kaplowitz N, DeLeve LD, eds. *Drug-induced liver disease.* 3rd ed. Amsterdam: Elsevier, 2013, pp. 605-20.

(Review of hepatotoxicity of oral contraceptive steroids including cholestasis, vascular disorders, benign tumors and hepatocellular carcinoma).

Levin ER, Vitex WS, Hammes SR. Estrogens and progestins. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. *Goodman & Gilman's the pharmacological basis of therapeutics.* 13th ed. New York: McGraw-Hill, 2018, pp. 803-32.

(Textbook of pharmacology and therapeutics).

Perez-Mera RA, Shields CE. Jaundice associated with norethindrone acetate therapy. *N Engl J Med.* 1962;267:1137–8. PubMed PMID: 13942388.

(35 year old woman developed jaundice and abdominal pain 2 years after starting norethindrone for dysmenorrhea with bilirubin 6.5 mg/dL, biopsy showing intrahepatic cholestasis and repeat biopsy 2 months after stopping estrogen showing resolution).

Eisalo A, Jaervinen PA, Luukkainen T. Hepatic impairment during the intake of contraceptive pills: clinical trial with postmenopausal women. *Br Med J.* 1964;2:426–7. PubMed PMID: 14160244.

(12 postmenopausal Finnish women were treated with progesterone or estrogen or both [Lyndiol] for 28 days; on estrogen [methoxy-ethynylestradiol], ALT elevations occurred in all patients with peak ALT 260-1900 U/L, bilirubin rise to 2.4 mg/dL in 1 and Alk P rise in 1, ALT usually peaking at 21-28 days, normalizing rapidly on stopping; no change on progesterone).

Adlercreutz H, Ikonen E. Oral contraceptives and liver damage. *Br Med J.* 1964;2:1133. PubMed PMID: 14198736.

(Letter in response to Eisalo et al.; mentions their own publications in Scandinavian literature, 3 cases of jaundice on OCCs, one had jaundice of pregnancy and repeated bouts of jaundice on various formulations of OCCs, degree of tolerance relating to estrogen content).

- Palva IP, Mustala OO. Oral contraceptives and liver damage. *Br Med J.* 1964;2:688–9. PubMed PMID: 14171108.
(*Five postmenopausal women were treated with OCCs [Anovlar: 4 mg norethisterone and 0.05 ethinyloestradiol]; AST levels rose in all five after 1 week with peak values 61-340 U/L, BSP raised in all and bilirubin in 2 patients; no mention of symptoms; laboratory abnormalities resolved slowly upon stopping*).
- Swaab LI. Oral contraceptives and liver damage. *Br Med J.* 1964;2:755. PubMed PMID: 14172046.
(*Analysis in 500 women taking two forms of OCCs; among 60 women who were monitored prospectively no elevations in AST or bilirubin levels were found*).
- Fawcett JW, Pederson DL. Oral contraceptives and liver damage. *Br Med J.* 1964;2:755. PubMed PMID: 14172046.
(*35 year old woman developed fever, rash and liver test abnormalities [bilirubin 5.9 mg/dL, ALT 260 U/L, Alk P 3 times ULN] during the 4th month of OCC use, resolving within 2 weeks, but no mention of whether OCCs were stopped*).
- Linthorst G. Liver function after long-term progestational treatment with and without estrogen. *Br Med J.* 1964;2:920–1. PubMed PMID: 14185660.
(*Among 300 women treated with Lyndiol OCCs, none developed jaundice; prospective study in 50 patients treated for 14 to 43 months found no confirmed abnormalities of liver tests*).
- Rice-Wray E. Oral contraceptives and liver damage. *Brit Med J.* 1964;2:1011. PubMed PMID: 14185627.
(*In studies of 56 women receiving Lyndiol as birth control, none developed ALT abnormalities during 3 to 12 cycles of therapy*).
- Sotaniemi E, Kreuz KE, Scheinin TM. Oral contraceptives and liver damage. *Br Med J.* 1964;2:1264–5. PubMed PMID: 14204544.
(*24 year old woman developed itching after 10 days on OCCs with subsequent jaundice [bilirubin 8.2 rising to 14.6 mg/dL, Alk P 1.5 rising to 3 times ULN, AST 40 U/L], biopsy showing intrahepatic cholestasis, resolving within 7 weeks of stopping*).
- Wetterberg L. Oral contraceptives and acute intermittent porphyria. *Lancet.* 1964;2:1178–9. PubMed PMID: 14213591.
(*26 year old woman with frequent attacks of porphyria developed nausea and abdominal pain on OCCs [bilirubin 0.3 mg/dL, ALT 450 U/L, normal Alk P], improved on stopping OCCs*).
- Borglin NE. Oral contraceptives and liver damage. *Br Med J.* 1965;1:1289. PubMed PMID: 14278822.
(*36 Swedish women [ages 22-44 years] with endometriosis were treated with lynoestrenol or Lyndiol for 3 months; ALT rose in 4 of 10 patients receiving Lyndiol with peak values of 42, 72, 310 and 430 U/L, resolving rapidly with stopping*).
- Gate JM. Oral contraceptives and liver injury. *Br Med J.* 1965;1:1672. PubMed PMID: 14295333.
(*Letter commenting that liver injury due to oral contraceptives may be underreported because of small studies of short term use*).
- Morton WA, Johnstone FR. Oral contraceptives and liver injury. *Br Med J.* 1965;1:1391. PubMed PMID: 14286994.
(*Editorial on the safety of OCCs; despite widespread use, the numbers of cases of frank liver injury attributed to them are few*).
- Boake WC, Schade SG, Morrissey JF, Schaffner F. Intrahepatic cholestatic jaundice of pregnancy followed by Enovid-induced cholestatic jaundice. *Ann Intern Med.* 1965;63:302–8. PubMed PMID: 14318470.

- (28 year old woman developed pruritus within 4 days of starting OCCs and later jaundice despite stopping [bilirubin 5.5 mg/dL, ALT 356 U/L, Alk P 2 times ULN], resolving slowly after stopping; had history of two episodes of jaundice during pregnancies: Case 1).
- Eisenstadt HB. Abnormal liver function and synthetic estrogens. JAMA. 1965;194:933. PubMed PMID: 5898078.
- (25 year old woman developed fatigue and nausea 9 months after starting OCCs [Ortho-Novum] with normal liver tests except BSP [18%] and liver biopsy showing excess lipofuscin, symptoms resolved with stopping pill).
- Cullberg G, Lundstrom R, Stenram U. Jaundice during treatment with an oral contraceptive, Lyndiol. Br Med J. 1965;1:695-7. PubMed PMID: 14245208.
- (39 year old woman developed nausea and pruritus within 10 days of starting OCC [bilirubin 8.4 mg/dL, ALT 230 U/L, Alk P 8 times ULN], resolution not mentioned).
- Stoll BA, Andrews JT, Motteram R, Upfill J. Oral Contraceptives and liver damage. Br Med J. 1965;1:723. PubMed PMID: 14245215.
- (Among 4 women given OCCs [6 pills daily] for breast cancer, all developed AST elevations >200 U/L after 2 weeks of therapy and two were jaundiced; biopsies showed centrilobular cholestasis and necrosis; resolving with stopping).
- Carlström H, Höglund S, Reizenstein P. Oral contraceptives and liver damage. Br Med J. 1965;1:993. PubMed PMID: 14260636.
- (38 year old woman with history of pruritus of pregnancy developed pruritus and jaundice after starting OCCs [bilirubin 6.1 mg/dL, Alk P 2 times ULN, eosinophils 18%], resolving with stopping drug).
- Larsson-Cohn U, Stenram U. Jaundice during treatment with oral contraceptive agents. Report of two cases. JAMA. 1965;193:422-6. PubMed PMID: 14326711.
- (Two women, ages 44 and 28 developed pruritus within 1-2 weeks of starting OCCs [bilirubin 3.0-7.0 mg/dL, ALT 480-730 U/L and Alk P 1-2 times ULN], resolving within 2-3 weeks of stopping; one had history of cholestasis of pregnancy).
- Oigaard A. Ugeskr Laeger. 1965;127(45):1444-6. [Jaundice following norethynodrel plus mestranol (enovid)]. Danish. PubMed PMID: 5868177.
- (21 year old woman developed jaundice within few weeks of starting OCCs [AST 107 U/L, Alk P 3 times ULN], biopsy showing intrahepatic cholestasis, slow recovery on corticosteroids).
- Elliott AJ, Hendry J. Cholestatic jaundice complicating pregnancy. Recurrence after norethynodrel with ethynylestradiol (Enovid). Can Med Assoc J. 1965;92:344-5. PubMed PMID: 14243870.
- (26 year old woman had marked pruritus during 3 pregnancies beginning ~6th month with jaundice that rapidly resolved with delivery; developed itching and jaundice within 2 weeks of starting OCCs [bilirubin 6.3 mg/dL, AST 50 U/L, Alk P 13.7 KA], resolving rapidly on stopping).
- Baines GF. Jaundice in a patient taking norethisterone compound tablets. Lancet. 1965;1(7376):108-9. PubMed PMID: 14234193.
- (Woman developed jaundice during second cycle of OCCs [bilirubin 7.5 mg/dL], resolving rapidly on stopping).
- Becker FT. Porphyria cutanea tarda induced by estrogens. Arch Dermatol. 1965;92:252-5.
- (Three cases of men given diethylstilbestrol for prostate cancer who developed porphyria cutanea tarda 8-48 months later).

Holzbach RT, Sanders JH. Recurrent intrahepatic cholestasis of pregnancy: observations on pathogenesis. JAMA. 1965;193:542-4. PubMed PMID: 14326722.

(32 year old woman developed severe, generalized pruritus in last trimester of 3 pregnancies, followed by mild jaundice during fourth pregnancy [bilirubin 4.0 mg/dL, AST 92 U/L, Alk P 3 times ULN] and then redeveloped symptoms and laboratory test abnormalities 1-2 weeks after starting OCCs; mother and sister had similar symptoms during pregnancies).

Perlroth MG, Marver HS, Tschudy DP. Oral contraceptive agents and the management of acute intermittent porphyria. JAMA. 1965;194:1037-42. PubMed PMID: 5897774.

(Report of three women with cyclic premenstrual exacerbations of porphyria in whom OCCs appeared to control symptoms).

von Oldershausen H-F, Eggstein M, Dold U, Knörr K. Dtsch Med Wochenschr. 1965;90:1290-4. [Icterus in intrahepatic cholestasis following the administration of contraceptive steroids]. German. PubMed PMID: 14315000.

(31 year old woman developed pruritus 3 weeks and jaundice 5 weeks after starting OCCs [bilirubin 6.9 mg/dL], resolving slowly after stopping [>3 months] despite corticosteroid therapy).

von Oldershausen HF, Eggstein M, Dold U, Knörr K. Intrahepatic cholestasis with jaundice after taking contraceptive steroids. Ger Med Mon. 1966;11:24-8. PubMed PMID: 5933450.

(English translation of von Oldershausen [1965] of 31 year old woman with cholestasis due to OCCs).

Schaffner F. The effect of oral contraceptives on the liver. JAMA. 1966;198:1019-21. PubMed PMID: 5332484.

(Review of literature on effects of OCCs on the liver and recommendations on their avoidance in women with history of jaundice of pregnancy, primary biliary cirrhosis and constitutional hyperbilirubinemia).

Ecker JA, McKittrick JE, Failing RM. Thrombosis of the hepatic veins. The Budd-Chiari syndrome a possible link between oral contraceptives and thrombosis formation. Am J Gastroenterol. 1966;45:429-43. PubMed PMID: 4952754.

(23 year old woman developed nausea and acute abdominal pain within weeks of starting OCCs with progression to massive ascites and hepatic failure; hepatic vein thrombosis found on autopsy).

Orellana-Alcalde JM, Dominguez JP. Jaundice and oral contraceptive drugs. Lancet. 1966;2:1279-80. PubMed PMID: 4163418.

(Over 50 women with jaundice on OCCs seen over a two year period in Santiago, Chile; geographic distribution similar to intrahepatic cholestasis of pregnancy; estrogen usually ethinylestradiol 0.05 mg or mestranol 0.15 mg daily; 17 of 42 had previous history of cholestasis during pregnancy; onset usually with first cycle; bilirubin 1.7-19.3 mg/dL, Alk P mildly elevated and ALT raised in two-thirds, some above 300 U/L; positive rechallenge in 6).

Thulin KE, Nermark J. Seven cases of jaundice in women taking oral contraceptive, Anovlar. Br Med J. 1966;1:584-6. PubMed PMID: 5907316.

(Six women on OCC [Anovlar] seen with jaundice in two month period; ages 19-37 years on OCCs for unknown duration [bilirubin 3.0-8.1 mg/dL, ALT 115-1600 U/L, Alk P 1-2 times ULN]; one had history of pruritus of pregnancy).

Copeman PW, Cripps DJ, Summerly R. Cutaneous hepatic porphyria and oestrogens. Br Med J. 1966;1:461-3. PubMed PMID: 5902684.

(Two men with prostate cancer treated with estrogen therapy developed cutaneous manifestations of porphyria, but with little change in serum, urine or fecal porphyrin excretion).

- Card IR, Sneddon IB, Talbot CH. Oral contraceptives and jaundice. *Br Med J.* 1966;1(5489):739–40. PubMed PMID: 5909490.
- (34 year old woman on OCCs for 2 years developed severe pruritus without jaundice [bilirubin 1.6-2.4 mg/dL, Alk P 1.5-2.5 times ULN], with resolution on stopping OCCs; had history of pruritus of pregnancy).*
- Kreek MJ, Weser E, Slesinger MH, Jefferies GH. Idiopathic cholestasis of pregnancy: the response to challenge with the synthetic estrogen, ethinyl estradiol. *N Engl J Med.* 1967;277:1391–5. PubMed PMID: 6081143.
- (7 women with a history of pruritus or jaundice of pregnancy and 6 controls were treated with ethinyl estradiol [0.5 to 1.5 mg daily] for up to two weeks; estrogens triggered symptoms of pruritus in most women with a history of cholestasis of pregnancy, marked rise in BSP retention and jaundice [bilirubin 2.4 mg/dL] in one; no change in the controls).*
- Sterup K, Mosbech J. Budd-Chiari syndrome after taking oral contraceptives. *BMJ.* 1967;4:660–2. PubMed PMID: 6059263.
- (28 year old woman taking OCCs for 12-18 months developed nausea and abdominal distention, with progressive ascites and variceal hemorrhage; autopsy showed hepatic vein thrombosis).*
- Medical Research Council. Risk of thromboembolic disease in women taking oral contraceptives. *Br Med J.* 1967;2:355. PubMed PMID: 6023133.
- (Two small case controlled studies in general practice population found link between OCCs and venous thrombosis and pulmonary embolus, but not coronary thrombosis).*
- Grayson MJ, Reilly MCT. Budd-Chiari syndrome after oral contraceptives. *BMJ.* 1968;1:512–3. PubMed PMID: 5643729.
- (37 year old woman on OCCs for a year developed pain and abdominal distension with acute Budd-Chiari syndrome and death).*
- Clubb AW, Giles C. Budd-Chiari syndrome in women taking oral contraceptives. *Br Med J.* 1968;1:252. PubMed PMID: 5634822.
- (40 year old woman on OCCs for 2 years underwent surgery for uterine fibroids and was found to have an enlarged liver developing progressive ascites in postoperative period leading to hepatic failure and death; autopsy showed thrombosis in hepatic veins).*
- Rothwell-Jackson RL. Budd Chiari syndrome after oral contraceptives. *Br Med J.* 1968;1:252. PubMed PMID: 5634821.
- (24 year old woman developed Budd-Chiari syndrome 4 months after starting OCCs, with progressive course and death, autopsy showing hepatic vein thrombosis).*
- Somayaji BN, Eeles GH, Paton A, Parker RGF. Budd-Chiari syndrome after oral contraceptives. *Br Med J.* 1968;1:53–4. PubMed PMID: 5636748.
- (39 year old woman developed Budd Chiari syndrome after taking OCCs for 2.5 years; improved without surgery on stopping OCCs).*
- Somayaji BN, Paton A, Price JH, Harris AW, Flewett TH. Norethisterone jaundice in two sisters. *Br Med J.* 1968;2:281–3. PubMed PMID: 4296504.
- (Two sisters developed jaundice and pruritus after taking OCCs or estrogens for 18 and 10 days [bilirubin 6.7 and 12.8 mg/dL, ALT 30 and 16 U/L, Alk P ~3 times ULN], with slow recovery on stopping pill; one had history of pruritus of pregnancy).*
- Chamberlain DW, Walter JB. The relationship of Budd-Chiari syndrome to oral contraceptives and trauma. *Can Med Assoc J.* 1969;101:97–100. PubMed PMID: 5348884.

- (37 year old on OCCs for two years developed acute Budd-Chiari syndrome after a motor vehicle accident and abdominal trauma).
- Irey NS, Manion WC, Taylor HB. Vascular lesions in women taking oral contraceptives. Arch Pathol. 1970;89:1–8. PubMed PMID: 4188605.
- (Analysis of arteries and veins from tissue specimens from 20 women who developed thromboembolism during OCC therapy [5 weeks to 13 months]; one had Budd Chiari syndrome, found locally formed thrombi rather than thromboembolus, changes in walls at site of thrombi suggesting that these were primary).
- Adlercreutz H, Tenhunen R. Some aspects of the interaction between natural and synthetic female sex hormones and the liver. Am J Med. 1970;49:630–8. PubMed PMID: 4924590.
- (Review of effects of estrogens on hepatic function in relationship to cholestasis of pregnancy and cholestasis induced by estrogens and OCCs).
- Kositchek RJ, Cullen RA. Hemangiomas of the liver with thrombosis following use of an oral contraceptive. Calif Med. 1970;113:70–4. PubMed PMID: 5457518.
- (36 year old woman on cyclic estrogen therapy for menorrhagia for 6 months developed hepatic mass, wedge biopsy showing hemangiomas, stable upon stopping therapy but few details given).
- Rowley PT, Kurnick J, Chevillat R. Hereditary haemorrhagic telangiectasia: aggravation by oral contraceptives. Lancet. 1970;1:474–5. PubMed PMID: 4189787.
- (Reports of three women who had worsening problems with telangiectasia after starting OCCs including increase in size and more frequent bleeding).
- Harris PW. Hereditary haemorrhagic telangiectasia and oral contraceptives. Lancet. 1970;1:615–6. PubMed PMID: 4190564.
- (Suggests that higher doses of estrogens are needed to control epistaxis and that lower doses might worsen telangiectasia).
- Blackburn EK. Hereditary haemorrhagic telangiectasia and oral contraceptives. Lancet. 1970;1:616. PubMed PMID: 4190565.
- (Comments on acne being worsened by some estrogen preparations).
- Harrison DF. Hereditary haemorrhagic telangiectasia and oral contraceptives. Lancet. 1970;1:721. PubMed PMID: 4191022.
- (Unlike Rowley et al, this investigator found improvement in bleeding episodes in patients with hereditary telangiectasia with estrogen or OCC therapy).
- Hoyumpa AM, Schiff L, Helfman EL. Budd-Chiari syndrome in women taking oral contraceptives. Am J Med. 1971;50:137–40. PubMed PMID: 5539574.
- (Two women developed Budd Chiari syndrome 3 weeks and 8 years after starting OCCs; one survived with diuretic therapy, the other died).
- Dooner HP, Hoyl C, Aliaga C, Parada J. Jaundice and oral contraceptives. Acta Hepatosplenol. 1971;18:84–94. PubMed PMID: 5552035.
- (Seven women who developed jaundice on OCCs, cholestatic in 6, details given in two patients).
- Kontturi M, Sotaniemi E, Ahlgvist J. Liver damage and estrogen therapy of prostatic cancer: case report. Scand J Urol Nephrol. 1972;6:289–94. PubMed PMID: 4629449.
- (Among 62 men with prostate cancer treated with diethylstilbestrol, 1 developed jaundice 40 days after starting [bilirubin 6.9 mg/dL, but normal ALT and Alk P], resolved on stopping, but later found to have cirrhosis).

Metreau JM, Dhumeaux D, Berthelot P. Oral contraceptives and the liver. *Digestion*. 1972;7:318–35. PubMed PMID: 4602326.

(Review of effects of OCCs on the liver; over 300 cases of jaundice due to OCCs have been reported with higher frequency in Chile and Scandinavia [1:4000 cases vs 1:10,000 elsewhere]; higher rate with early OCCs such as Lyndiol, Anovlar and Enovid compared to later, lower dose preparations).

Johnson FL, Lerner KG, Siegel M, Feagler JR, Majerus PW, Hartmann JR, Thomas ED. Association of androgenic-anabolic steroid therapy with the development of hepatocellular carcinoma. *Lancet*. 1972;2:1273–6. PubMed PMID: 4117807.

(Description of 4 cases of hepatocellular carcinoma related to C17-alkylated anabolic steroids given for aplastic anemia or Fanconi syndrome, 2 females and 2 males, ages 5 to 27 years taking drugs for 1-7 years; regression of tumor in one after withdrawal but all died within one year).

Cohen L, Lewis C, Arias IM. Pregnancy, oral contraceptives, and chronic familial jaundice with predominantly conjugated hyperbilirubinemia (Dubin-Johnson syndrome). *Gastroenterology*. 1972;62:1182–90. PubMed PMID: 5050316.

(Among 101 patients seen for jaundice during pregnancy or OCC use, 27 had Dubin-Johnson syndrome, marked by normal serum enzymes and bile acids; onset of jaundice during first 3 cycles of OCCs or late in pregnancy, rapid reversal with stopping or delivery; family studies suggested autosomal recessive inheritance; liver biopsies were black with pericanalicular black pigment).

Rencoret R, Aste H. Jaundice during pregnancy. *Med J Aust*. 1973;1:167–9. PubMed PMID: 4694270.

(32 cases of jaundice during pregnancy, 0.43% of all pregnancies [Chile]; usually arising in 3rd trimester, 50% recurrence after initial episode; pruritus followed in 2-3 weeks by jaundice, but bilirubin rarely above 5.0 mg/dL, Alk P elevated 1-6 times ULN and ALT elevations up to 176 U/L, often leading to prematurity, resolves rapidly with delivery; no maternal deaths).

Baum JK, Brookstein JJ, Holtz F, Klein EW. Possible association between benign hepatomas and oral contraceptives. *Lancet*. 1973;2:926–9. PubMed PMID: 4126557.

(Seven cases of hepatic adenoma in woman on OCCs for 0.5-7 years, ages 25 to 39 years, 5 with rupture, one fatal).

Contostavlos DL. Benign hepatomas and oral contraceptives. *Lancet*. 1973;2:1200. PubMed PMID: 4127562.

(37 year old woman on OCCs for many years developed acute epigastric pain and died suddenly, autopsy showing large adenoma).

Boston Collaborative Drug Surveillance Programme. Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumours. *Lancet*. 1973;1:1399–404. PubMed PMID: 4126154.

(Hospital based survey of women ages 20 to 44 years found higher rates of OCC use among those with diagnosis of venous thromboembolism [72% vs 20% in controls] and gallbladder disease [31% vs 20%], but not breast tumors).

Boston Collaborative Drug Surveillance Program. Surgically confirmed gallbladder disease, venous-thromboembolism and breast tumors in relation to postmenopausal estrogen therapy. *N Engl J Med*. 1974;290:15–9. PubMed PMID: 4357161.

(Hospital based survey of 5339 postmenopausal women, ages 45 to 69 years, found higher rate of gall bladder disease in women on estrogens; relative risk of 2.5, but no association of estrogen use with thromboembolism or breast cancer).

Berg JW, Ketalaar RJ, Rose EF, Vernon RG. Letter. Hepatomas and oral contraceptives. *Lancet*. 1974;2:349–50. PubMed PMID: 4136079.

(During 3 year period, 4 women with hepatic adenomas were entered in an Iowa State registry, ages 23 to 32 years, 3 on OCCs and one pregnant; no cases in previous 35 years).

O'Sullivan JP, Wilding RP. Liver hamartomas in patients on oral contraceptives. *Br Med J.* 1974;3:7–10. PubMed PMID: 4835461.

(3 cases of liver tumors arising in 34, 35 and 51 year old women on OCCs for 4-8 years, referred to as hamartomas, but later said to be more likely adenomas).

Thalassinos NC, Lymberatos C, Hadjioannou J, Gardikas C. Liver-cell carcinoma after long-term oestrogen-like drugs. *Lancet.* 1974;1:270–1. PubMed PMID: 4130278.

(30 year old woman treated with estrogens for infertility developed 5 cm hepatocellular carcinoma shortly after delivery).

Kelso DR. Benign hepatomas and oral contraceptives. *Lancet.* 1974;1:315–6. PubMed PMID: 4130500.

(36 year old woman on OCCs for 5 years had acute hemoperitoneum from large hepatic adenoma and died).

Meyer P, Livolsi VA, Cornog JL. Hepatoblastoma associated with an oral contraceptive. *Lancet.* 1974;2:1387. PubMed PMID: 4143346.

(19 year old woman on OCCs for 9 months developed fever and abdominal pain and found to have a 17 cm locally invasive hepatoblastoma).

Tountas C, Paraskevas G, Deligeorgi H. Benign hepatoma and oral contraceptives. *Lancet.* 1974;1:1351–2. PubMed PMID: 4134336.

(30 year old woman on OCCs for 3 years had successful resection of hepatic adenoma).

Dalén E, Westerholm B. Occurrence of hepatic impairment in women jaundiced by oral contraceptives and in their mothers and sisters. *Acta Med Scand.* 1974;195:459–63. PubMed PMID: 4835153.

(Questionnaire from 141 women with OCC associated jaundice and 210 controls on OCCs without problems; 47% of patients had pruritus and 6% jaundice during pregnancy compared to 11% and 0 in controls; also higher rate of gallstones [20% vs 4%], and pruritus/jaundice during pregnancy [15% vs 1%] among siblings of patients compared to controls).

Drill VA. Benign cholestatic jaundice of pregnancy and benign cholestatic jaundice from oral contraceptives. *Am J Obstet Gynecol.* 1974;119:165–74. PubMed PMID: 4595936.

(Review of clinical presentation and pathogenesis of cholestasis of pregnancy and OCCs).

Morley JE, Myers JB, Sack PS, Kalk F, Epstein EE, Lannon J. Enlargement of cavernous haemangioma associated with exogenous administration of oestrogens. *S Afr Med J.* 1974;48:695–7. PubMed PMID: 4363028.

(57 year old woman developed enlarging hepatic mass on estrogens; 950 gram cavernous hemangioma).

Frederick WC, Howard RG, Spatola S. Spontaneous rupture of the liver in a patient using contraceptive pills. *Arch Surg.* 1974;108:93–5. PubMed PMID: 4808582.

(28 year old woman on OCCs for 14 months presented with spontaneous rupture of liver; resected lobe showed hepatic vein thrombosis without tumor).

Knapp WA, Ruebner BH. Hepatomas and oral contraceptives. *Lancet.* 1974;1:270–1. PubMed PMID: 4130279.

(33 year old woman on OCCs for several years presented with acute abdomen and was found to have large adenoma, died postoperatively).

Horvath E, Kovacs K, Ross RC. Letter: Benign hepatoma in a young woman on contraceptive steroids. *Lancet.* 1974;1:357–8. PubMed PMID: 4131203.

(28 year old on OCCs for 7 years had adenoma, on electron microscopy cells had crystalloid inclusions in mitochondria).

Albritton DR, Tompkins RK, Longmire WP Jr. Hepatic cell adenoma: a report of four cases. *Ann Surg.* 1974;180:14–9. PubMed PMID: 4366047.

(Four cases of hepatic adenoma undergoing resection; no mention of OCCs).

Mays ET, Christopherson WM, Burrows GH. Focal nodular hyperplasia of the liver – possible relationship to oral contraceptives. *Am J Clin Pathol.* 1974;61:735–6. PubMed PMID: 4364925.

(Three women on OCCs for 4-7 years found to have large hepatic masses after presenting with pain or hemoperitoneum; appeared to be focal nodular hyperplasia rather than adenomas).

Winkler K, Poulsen H. Liver disease with periportal sinusoidal dilatation. *Scand J Gastroenterol.* 1975;10:699–704. PubMed PMID: 1188303.

(Four women on OCCs who underwent liver biopsy for different indications were found to have sinusoidal dilatation in periportal [zone 1] areas).

Christopherson WM, Mays ET, Barrows GH. Liver tumors in women on contraceptive steroids. *Obstet Gynecol.* 1975;46:221–3. PubMed PMID: 168523.

(Pathology report on 13 cases of liver tumors in women on OCCs including 8 with focal nodular hyperplasia, 3 hamartoma, 1 adenoma and 1 carcinoma).

Davis M, Portmann B, Searle M, Wright R, Williams R. Histological evidence of carcinoma in a hepatic tumour associated with oral contraceptives. *Br Med J.* 1975;4:496–8. PubMed PMID: 172187.

(21 year old woman on OCCs for 2 years found to have 820 g hepatic mass which had histological features of focal nodular hyperplasia and hepatocellular carcinoma; only short term follow up given).

Antoniades K, Brooks CE Jr. Hemoperitoneum from liver cell adenoma in a patient on oral contraceptives. *Surgery.* 1975;77:137–9. PubMed PMID: 162813.

(30 year old woman had spontaneous rupture of 6.5 cm adenoma 5 weeks after third pregnancy; history of OCC use for 4 years).

Antoniades K, Campbell WN, Hecksher RH, Kessler WB, McCarthy GE. Liver cell adenoma and oral contraceptives: double tumor development. *JAMA.* 1975;234:628–9. PubMed PMID: 170431.

(32 year old woman on OCCs for 6 years presented with abdominal pain and found to have two hepatic masses, 14 and 7.5 cm hepatic adenomas).

Ameriks JA, Thompson NW, Frey CF, et al. Hepatic cell adenomas. Spontaneous liver rupture and oral contraceptives. *Arch Surg.* 1975;110:548–57. PubMed PMID: 1131000.

(Review of 8 cases of hepatic adenoma seen in 5 years at one center; all were women, ages 25 to 44 years taking OCCs for 6 months to 9 years).

Stenwig AE, Solgaard T. Ruptured benign hepatoma associated with an oral contraceptive. A case report. *Virchows Arch A Pathol Anat Histol.* 1975;367:337–43. PubMed PMID: 170733.

(Rupture of hepatic adenoma late in pregnancy of a woman who had been on OCCs for 8 years).

Grabowski M, Stenram U, Bergvist A. Focal nodular hyperplasia of the liver, benign hepatomas, oral contraceptives and other drugs affecting the liver. *Acta Pathol Microbiol Scand A.* 1975;83:615–22. PubMed PMID: 171910.

(Retrospective review of pathology files from two hospitals identified 18 cases of focal nodular hyperplasia and 2 cases of adenoma in women; half were taking OCCs).

Langlands AO, Martin WM. Jaundice associated with norethisterone-acetate treatment of breast cancer. *Lancet*. 1975;1:584–5. PubMed PMID: 47070.

(107 patients with breast cancer were treated with progesterone derivative; 6 developed jaundice within 4 months with elevations in ALT [192-287 U/L] and Alk P [1-5 times ULN] and mild jaundice that resolved with stopping).

Stauffer JQ, Lapinski MW, Honold DJ, Myers JK. Focal nodular hyperplasia of the liver and intrahepatic hemorrhage in young women on oral contraceptives. *Ann Intern Med*. 1975;83:301–6. PubMed PMID: 1180424.

(Three women presenting with pain and liver masses on long term OCCs [6-7 years] found to have focal nodular hyperplasia on resection).

Knowles DM, Wolff M. Systemic contraceptives and the liver. *Ann Intern Med*. 1975;83:907–8. Letter. PubMed PMID: 173222.

(Letter to editor in response to Stauffer [1975] stressing the importance but difficulty in separating adenomas from focal nodular hyperplasia).

Haberman HF, Rosenberg F, Menon IA. Porphyria cutanea tarda: comparison of cases precipitated by alcohol and estrogens. *Can Med Assoc J*. 1975;113:653–5. PubMed PMID: 1181022.

(7 patients with porphyria cutanea tarda [PCT] precipitated by alcohol were compared to 9 patients with PCT precipitated by estrogens; similar clinical features; estrogens taken for 7 months to 14 years; some, but not all had AST elevations or high iron indices; stopping estrogens reversed symptoms in only one patient; all responded to phlebotomy).

Glassberg AB, Rosenbaum EH. Letter: Oral contraceptives and malignant hepatoma. *Lancet*. 1976;1:479. PubMed PMID: 55736.

(31 year old woman on OCCs for 11 years was found to have a large hepatic mass and secondary lesions shown histologically to be hepatocellular carcinoma; no details of follow up given).

Hilliard JL, Graham DY, Spjut HJ. Hepatic adenoma: a possible complication of oral contraceptive therapy. *South Med J*. 1976;69:683–7. PubMed PMID: 935896.

(Three cases of hepatic adenomas in women, two on OCCs for 1.2 and 4 years).

Kalra TM, Mangla JC, DePapp EW. Benign hepatic tumors and oral contraceptive pills. *Am J Med*. 1976;61:871–7. PubMed PMID: 188336.

(10 year retrospective review of records from 5 hospitals; found 7 adenomas, 5 in young women [ages 29 to 40 years] on OCCs and 2 cases of peliosis in 8 and 64 year olds, both with aplastic anemia on androgenic steroids).

Lansing PB, McQuitty JT, Bradburn DM. Benign liver tumors: what is their relationship to oral contraceptives? *Am Surg*. 1976;42:744–60. PubMed PMID: 184729.

(Between 1952-75, authors identified 3 cases of adenoma and 5 of focal nodular hyperplasia, 7 in women, all survived after resection; 5 had taken OCCs).

Tigano F, Ferlazzo B, Barrile A. Oral contraceptives and malignant hepatoma. *Lancet*. 1976;2:196. PubMed PMID: 73812.

(22 year old woman on OCCs for 2 years developed hepatocellular carcinoma and died; viral markers not reported).

McAvoy JM, Tompkins RK, Longmire WP. Benign hepatic tumors and their association with oral contraceptives. *Arch Surg*. 1976;111:761–7. PubMed PMID: 180932.

(Two women on OCCs for 15 and 9 years presented with large hepatic masses, found to be adenoma on resection: review of literature).

Andersen PH, Packer JT. Hepatic adenoma: observations after estrogen withdrawal. *Arch Surg.* 1976;111:898–900. PubMed PMID: 182106.

(24 year old woman on OCCs for 20 months presented with hepatic rupture and biopsy showed adenoma, but tumor incompletely resected; OCCs stopped and tumor decreased in size, but ultimately required resection 18 months later).

Brander WL, Vosnides G, Ogg CS, West IE. Multiple hepatocellular tumors in a patient treated with oral contraceptives. *Virchows Arch A Pathol Anat Histol.* 1976;370:69–76. PubMed PMID: 179194.

(24 year old woman with chronic renal failure developed large liver and spontaneous rupture; autopsy showed 5 kg liver with multiple adenomas).

Edmondson HA, Reynolds TB, Henderson B, Benton B. Liver cell adenomas associated with use of oral contraceptives. *N Engl J Med.* 1976;294:470–2. PubMed PMID: 173996.

(Analysis of 42 women with hepatic adenomas and matched controls; OCC use was common [85 vs 70%] and used for longer in those with adenomas [80 vs 38 months] and higher mestranol vs ethinyl estradiol use).

Mays ET, Christopherson WM, Mahr MM, Williams HC. Hepatic changes in young women ingesting contraceptive steroids: hepatic hemorrhage and primary tumors. *JAMA.* 1976;235:730–2. PubMed PMID: 175178.

(Review of 13 women presenting with liver tumors on OCCs seen between 1968-74; none had cirrhosis; 9 tumors were benign [mostly focal nodular hyperplasia; all alive] and 4 malignant [hepatocellular carcinoma; 3 died]; 6 presented with rupture, one tumor recurred in woman who continued OCC use).

Ross D, Pina J, Mirza M, Galvan A, Ponce L. Letter: Regression of focal nodular hyperplasia after discontinuation of oral contraceptives. *Ann Intern Med.* 1976;85:203–4. PubMed PMID: 942141.

(25 year old woman on OCCs for 6 years presented with several hepatic masses, one resected showed probable adenoma, the other regressed in size during follow up off of OCCs).

Goldfarb S. Sex hormones and hepatic neoplasia. *Cancer Res.* 1976;36:2584–8. PubMed PMID: 179705.

(Review of literature and 6 cases of liver tumors related to estrogens and OCCs: among 40 cases in the literature, 25 were called adenoma, 13 focal nodular hyperplasia, 3 hamartomas, 3 carcinoma and 1 hepatoblastoma; a major problem was lack of consistency in histologic criteria for diagnosis).

Alpert LI. Venous-occlusive disease of the liver associated with oral contraceptives. Case report and review of literature. *Hum Pathol.* 1976;7:709–18. PubMed PMID: 992650.

(36 year old woman on OCCs for 4 years developed ascites, esophageal varices and progressive hepatic failure; autopsy showed hepatic vein thrombosis and obliteration of hepatic veins suggestive of venous-occlusive disease).

de Pagter AG, van Berge Henegouwen GP, ten Bokkel Huinink JA, Brandt KH. Familial benign recurrent intrahepatic cholestasis. Interrelation with intrahepatic cholestasis of pregnancy and from oral contraceptives? *Gastroenterology.* 1976;71:202–7. PubMed PMID: 939378.

(Study of a family with 4 members with benign recurrent intrahepatic cholestasis [BRIC], 9 with cholestasis of pregnancy and two with cholestasis on OCCs; one BRIC patient had recurrent episodes of cholestasis during pregnancies; suggesting shared pathogenesis of these three cholestatic syndromes).

Medline A, Ptak T, Gryfe A, Blenkinsop B. Pruritus of pregnancy and jaundice induced by oral contraceptives. *Am J Gastroenterol.* 1976;65:156–9. PubMed PMID: 1274944.

(18 year old woman developed jaundice 1 month after starting OCCs and then pruritus of pregnancy in third trimester; jaundice recurrence on restarting OCCs which were continued until bilirubin reached 37 mg/dL, AST 114 U/L, Alk P 306 U/L, resolving on stopping).

Edmondson HA, Reynolds TB, Henderson B, Benton B. Regression of liver cell adenomas associated with oral contraceptives. *Ann Intern Med.* 1977;86:180–2. PubMed PMID: 835939.

(Three women on OCCs for 4-13 years found to have multiple or unresectable hepatic adenomas with regression after stopping).

Leissner KH, Wedel H, Scherstein T. Comparison between the use of oral contraceptives and the incidence of surgically confirmed gallstone disease. *Scand J Gastroenterol.* 1977;12:893–6. PubMed PMID: 594657.

(Analysis of cholecystectomy rates in Sweden from 1961-71; there was an increase in rates in women who were 20-54 years old, suggestive of an effect of introduction of OCCs in early 1960s).

Christopherson WM, Mays ET. Liver tumors and contraceptive steroids: experience with the first one hundred registry patients. *J Natl Cancer Inst.* 1977;58:167–71. PubMed PMID: 189044.

(Analysis of first 100 patients in a registry of liver tumors in women found 40 adenomas, 44 focal nodular hyperplasias, 13 liver cancers and 4 unclassified tumors, mean age 30 years [14 to 47 years], only 4 were never on OCCs, pregnant or on estrogens [4-156 months]; presenting as hemoperitoneum [26%], pain [32%], mass [19%] or incidental finding [20%]).

Nissen ED, Kent DR, Nissen SE. Etiologic factors in the pathogenesis of liver tumors associated with oral contraceptives. *Am J Obstet Gynecol.* 1977;127:61–6. PubMed PMID: 188339.

(Registry of liver tumors and review of literature identified 71 cases of benign liver tumors associated with OCCs).

Aldinger K, Ben-Manachem Y, Whalen G. Focal nodular hyperplasia of the liver associated with high-dosage estrogens. *Arch Intern Med.* 1977;137:357–9. PubMed PMID: 190958.

(32 year old woman on estrogens after oophorectomy developed enlarging hepatic mass; on resection 4 years later it was at 10 cm focal nodular hyperplasia; on continuing estrogens she developed further hepatic masses than regressed when estrogens were stopped).

Klatskin G. Hepatic tumors. Possible relationship to use of oral contraceptives. *Gastroenterology.* 1977;73:386–94. PubMed PMID: 194813.

(Between 1973-75, reports of 237 hepatic tumors in women on OCCs; 44% adenomas, 35% focal nodular hyperplasia, 8% hepatocellular carcinoma; among benign tumors, 93% survival, recurrence only in patients who continued OCCs; among malignant tumors, survival ~50%, recurrence uncommon; discusses difficulty in diagnosis of adenoma vs focal nodular hyperplasia even with strict criteria).

Vana J, Murphy GP, Aronoff BL, Baker HW. Study of association between liver tumors and oral contraceptive use. *JAMA.* 1977;238:2154–8. PubMed PMID: 199752.

(American College of Surgeon's survey for 1970-75 identified 212 benign tumors in women; 96 adenomas and 58 focal nodular hyperplasia; OCC use reported in 74% of women with both types of tumors, but no evidence of dose-response; increase in yearly numbers of benign tumors between 1970 [n=22] and 1975 [n=47]).

Blayney AW, O'Callaghan T, MacErlean DP, O'Connell TC. Fatal outcome of an hepatic adenoma follow short term oral contraceptive use. *Ir Med J.* 1977;70:455–6. PubMed PMID: 924751.

(30 year old on OCCs for 18 months presented with intrahepatic bleed due to 12 cm hepatic adenoma in normal liver; sudden death).

Kay S. Nine-year follow up of a case of benign liver cell adenoma related to oral contraceptives. *Cancer.* 1977;40:1759–60. PubMed PMID: 198104.

(26 year old woman on OCC developed adenoma that was successfully resected, recurrence at 3 years during continuation of OCCs and regression over 6 years with stopping).

Anonymous. Liver tumours and the pill. *Br Med J.* 1977;2:345–6. PubMed PMID: 890288.

(Editorial on association of OCC and liver tumors: over 200 cases reported usually in long-term users of OCC with no accompanying liver disease).

Barrows GH, Christopherson WM, Drill VA. Liver lesions and oral contraceptive steroids. *J Toxicol Environ Health.* 1977;3:219–30. PubMed PMID: 926189.

(No increase in hepatic tumors in two strains of mice given OCCs).

Wu SM, Spurny OM, Klotz AP. Budd-Chiari syndrome after taking oral contraceptives. A case report and review of 14 reported cases. *Am J Dig Dis.* 1977;22:623–8. PubMed PMID: 879128.

(24 year old woman on OCCs for 4 years presented with abdominal pain and ascites and found to have Budd Chiari syndrome).

Pryor AC, Cohen RJ, Goldman RL. Hepatocellular carcinoma in a woman on long-term oral contraceptives. *Cancer.* 1977;40:884–8. PubMed PMID: 196746.

(32 year old woman on OCCs for 12 years presented with large hepatocellular carcinoma and died 1.5 years later of disease progression).

Chan CK, Detmer DE. Proper management of hepatic adenoma associated with oral contraceptives. *Surg Gynecol Obstet.* 1977;144:703–6. PubMed PMID: 66762.

(In instances without rupture, authors recommend stopping OCCs and observation, reserving resection for large tumors to be done by experienced surgeons only).

Fechner RE. Benign hepatic lesions and orally administered contraceptives: a report of severe cases and a critical analysis of the literature. *Hum Pathol.* 1977;8:255–68. PubMed PMID: 192659.

(Case series and clinical description of 12 young women with benign hepatic tumors; 6 adenomas [5 on OCCs] and 6 focal nodular hyperplasia [2 on OCCs], and extensive review of the literature).

Jick H, Herman R. Oral contraceptive-induced benign liver tumors-the magnitude of the problem. *JAMA.* 1978;240:828–9. PubMed PMID: 671723.

(From 2 retrospective studies, estimates were made that 100-140 U.S. women on OCCs developed hepatic tumors each year since 1970; or 1:80,000 users).

Kent DR, Nissen ED, Nissen SE, Ziehm DJ. Effect of pregnancy on liver tumor associated with oral contraceptives. *Obstet Gynecol.* 1978;51:148–51. PubMed PMID: 622225.

(Among 80 cases of liver tumors in OCC users in a registry, 4 cases had complications of adenomas during pregnancy, 2 presenting with rupture and 2 with enlarging mass and pain, usually during last trimester, suggesting that pregnancy is associated with tumor growth).

Trias R, Rius X, Autonell J, Algaba F. Hepatocarcinoma and oral contraceptives. *Lancet.* 1978;1:821. PubMed PMID: 85833.

(28 year old woman on OCCs for 13 months presented with 18 cm hepatocellular carcinoma with normal remaining liver).

Taxy JB. Peliosis. A morphologic curiosity becomes an iatrogenic problem. *Hum Pathol.* 1978;9:331–40. PubMed PMID: 658966.

(Five patients presenting with peliosis hepatis [4 with splenic involvement], all had received androgenic steroids or chemotherapy for lymphoma or myeloproliferative diseases).

- Nime F, Pickren JW, Vana J, Aronoff BL, Baker HW, Murphy GP. The histology of liver tumors in oral contraceptive users during a national survey by the American College of Surgeons Commission on Cancer. *Cancer*. 1979;44:1481–9. PubMed PMID: 227566.
- (Analysis of 94 submitted slides from liver tumors; 39% adenomas, 56% focal nodular hyperplasia [FNH]; all reported hamartomas were considered to be FNH; adenomas were larger than FNH and found only in OCC users, whereas FNH cases in OCC users had more vascular changes including peliosis).*
- Rooks JB, Ory HW, Ishak KG, Straus LT, Greenspan JR, Hill AP, Tyler CW Jr; Cooperative Liver Tumor Study Group. Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. *JAMA*. 1979;242:644–8. PubMed PMID: 221698.
- (Case control study of 79 young women with hepatic adenomas from the files of the Armed Forces Institute of Pathology compared to 299 controls, found increasing relative risk with long term OCC use from 1 ≤12 months to 129 for greater than 5 years; rate estimate of 3.4/100,000 patient years).*
- Pollak H. *MMW Munch Med Wochenschr*. 1979;121:93–4. [Spontaneous rupture of a liver adenoma following many years' ingestion of an oral contraceptive]. PubMed PMID: 105267.
- (34 year old woman on OCCs for 10 years developed sudden onset of right upper quadrant pain and shock and was found to have ruptured adenoma).*
- Sabriá Leal M, Mateu Ratera M, Canals Cadafalch J, Blanch Mortes MD, Munuera Gifre E. *Med Clin (Barc)*. 1979;73:234–8. [Hepatic adenomas and oral contraceptives. Report of two cases and review of the literature]. PubMed PMID: 547127.
- (Two women, ages 30 and 35 years, on OCCs for 4 and 5 years, presented with pain and hepatic mass, found to have large hepatic adenomas).*
- Ham JM, Fracs F, Pirola RC, Couch RL. Hemangioendothelial sarcoma of the liver associated with long-term estrogen therapy in a man. *Dig Dis Sci*. 1980;25:879–83. PubMed PMID: 7438959.
- (81 year old man with prostate cancer treated with stilbestrol for 9 years presented with pain and jaundice with bilirubin 4.1 mg/dL, mass on liver scan and autopsy showing large tumor consisting of large vascular spaces "hemangioendothelial sarcoma").*
- Bartók I, Decastello A, Csikós F, Nagy I. Focal nodular hyperplasia of the liver and hepatic cell adenoma in women on oral contraceptives. *Hepatogastroenterology*. 1980;27:435–40. PubMed PMID: 6259038.
- (Two women, ages 34 and 41 years, had onset of abdominal pain after 5 and 10 years of OCC use and found to have hepatic masses; one a 6 cm mass of focal nodular hyperplasia; the second a 19 cm adenoma; both successfully resected).*
- Neuberger J, Portmann B, Nunnerley HB, Laws JW, Davis M, Williams R. Oral-contraceptive-associated liver tumours: occurrence of malignancy and difficulties in diagnosis. *Lancet*. 1980;1:273–6. PubMed PMID: 6101735.
- (Experience at King's College Liver Unit, London between 1970-79; 10 women ages 12 to 42 years were found with hepatic tumors who had been on OCCs for 4-12 years, 7 were hepatocellular carcinoma; usually had Alk P elevations, minimal increases in AST; alpha-fetoprotein was always normal; 4 died of metastatic disease).*
- Littlewood ER, Harrison IG, Murray-Lyon IM, Paradinas FJ. Cholangio-carcinoma and oral contraceptives. *Lancet*. 1980;1:310–1. PubMed PMID: 6101761.
- (21 year old on OCCs for 5 years found to have cholangiocarcinoma; HBsAg and alpha-fetoprotein negative; no follow up given).*

- Camilleri M, Schafler K, Chadwich VS, Hodgson JH, Weinbren K. Periportal sinusoidal dilatation, inflammatory bowel disease, and the contraceptive pill. *Gastroenterology*. 1981;80:810–5. PubMed PMID: 6110610.
- (Two women, ages 19 and 28 year old, developed fatigue, diarrhea and weight loss 1.5 and 7 years after starting OCCs [bilirubin normal, AST 60 U/L and normal, Alk P 186 and 204 U/L], with hepatomegaly and liver biopsy showing periportal peliosis; symptoms [including diarrhea] and liver test abnormalities resolving within 2-4 weeks on stopping OCCs).*
- Tesluk H, Lawrie J. Hepatocellular adenoma: its transformation to carcinoma in a user of oral contraceptives. *Arch Pathol Lab Med*. 1981;105:296–99. PubMed PMID: 6263214.
- (34 year old woman on OCCs for 5 years presented with 14 cm adenoma which regressed in size with stopping; 3 years later the tumor began to grow and she underwent resection which showed hepatocellular carcinoma; patient died due to surgical complications).*
- Christensen SE, Andersen VR, Vilstrup H. A case of hepatoma in pregnancy associated with earlier oral contraception: a case report. *Acta Obstet Gynecol Scand*. 1981;60:519. PubMed PMID: 6272530.
- (45 year old woman developed hepatocellular carcinoma in last trimester of pregnancy; had taken OCCs for 5 years, 8 years before presentation).*
- Penkava RR, Rothenberg J. Spontaneous resolution of oral contraceptive-associated liver tumor. *J Comput Assist Tomogr*. 1981;5:102–3. PubMed PMID: 6263956.
- (55 year old woman presented with rupture of hepatic adenoma after 10 years of OCC use, repeat CT scans in follow up showed shrinkage after stopping).*
- Monroe PS, Roddell RH, Siegler M, Baker AL. Hepatic angiosarcoma: possible relationship to oral contraceptive ingestion. *JAMA*. 1981;246:64–5. PubMed PMID: 7195435.
- (32 year old woman on OCCs for 8 years developed multiple hepatic masses; surgery showed angiosarcoma [factor VIII positive]; tumor remained stable after stopping OCCs).*
- Porter JB, Jick H, Ylvisaker JT. Malignant liver tumor associated with oral contraceptive use. *Pharmacotherapy*. 1981;1:160. PubMed PMID: 6100817.
- (38 year old woman on OCCs for 10 years presented with abdominal mass found on autopsy to be cholangiocarcinoma).*
- Capron J-P, Lemay J-L, Muir J-F, Dupas JL, Lebrec D, Gineston JL. Portal vein thrombosis and fatal pulmonary thromboembolism associated with oral contraceptive treatment. *J Clin Gastroenterol*. 1981;3:295–8. PubMed PMID: 6974749.
- (33 year old woman on OCCs for 8 years found to have portal vein thrombosis and varices; died of multiple pulmonary emboli; likely had hypercoagulable state).*
- Balázs M, Kovách G, Winkler G, Jánosy J. *Dtsch Med Wochenschr*. 1981;106:1345–9. [Dilatation of hepatic sinusoids after use of oral contraceptives (author's transl)]. PubMed PMID: 7274083.
- Steinbrecher UP, Lisbona R, Huang SN, Mishkin SI. Complete regression of hepatocellular adenoma after withdrawal of oral contraceptive use. *Dig Dis Sci*. 1981;26:1045–50. PubMed PMID: 6271517.
- (28 year old woman on OCCs for 10 years presented with hepatic adenoma which regressed within 12 months of stopping: Case 3).*
- Thung SN, Gerber MA. Precursor stage of hepatocellular neoplasm following long exposure to orally administered contraceptives. *Hum Pathol*. 1981;12:472–4. PubMed PMID: 7195872.

(32 year old woman with Crohn's disease on OCCs for 10 years found to have Alk P 600 U/L, ALT 25 U/L, bilirubin 1.0 mg/dL and biopsy showing peliosis, increased reticulum and thick walled arteries and fibrosis in portal areas).

Ishak KG. Hepatic lesions caused by anabolic and contraceptive steroids. *Semin Liver Dis.* 1981;1:116–28. PubMed PMID: 6287645.

(Review of histologic effects of male and female sex hormones on the liver including biochemical changes, subcellular alternations, cholestasis, vascular disorders, hyperplasia, neoplasia and miscellaneous).

Shi EC, Fischer A, Crouch R, Ham JM. Possible association of angiosarcoma with oral contraceptive agents. *Med J Aust.* 1981;1:473–4. PubMed PMID: 7195976.

(42 year old woman who had taken OCCs for 10 years presented one year after stopping with unresectable hepatic mass; 15 cm angiosarcoma on autopsy).

Mettlin C, Nachimuthu N. Studies on the role of oral contraceptive use in the etiology of benign and malignant liver tumors. *J Surg Oncol.* 1981;18:73–85. PubMed PMID: 6270469.

(Chronological review of the literature linking OCCs and hepatic tumors; case-control studies have demonstrated a clear relationship of OCCs and hepatic adenomas, associated with longer duration of use and perhaps type of OCC; OCCs may also predispose to rupture and perhaps promote growth of unrelated benign lesions; their oncogenic potential requires further investigation).

Lockhat D, Katz SS, Lisbona R, Mishkin S. Oral contraceptives and liver disease. *Can Med Assoc J.* 1981;124:993–9. PubMed PMID: 7260802.

(19 year old woman on OCCs for 2.5 years developed abdominal pain and bloating [bilirubin 1.8 mg/dL, Alk P 114 U/L, ALT 35 U/L]; fluid in peritoneum and biopsy showed Budd-Chiari syndrome, with subsequent improvement after porto-caval shunt).

Schonberg LA. Peliosis hepatitis and oral contraceptives. A case report. *J Reprod Med.* 1982;27:753–6. PubMed PMID: 7161757.

(36 year old woman developed tender liver with normal serum enzymes; laparotomy showed ascites and hepatomegaly, while liver biopsy showed peliosis hepatitis; OCCs stopped, but no follow up given).

Royal College of General Practitioners Oral Contraception Study. Oral contraceptives and gallbladder disease. *Lancet.* 1982;2:957–9. PubMed PMID: 6127462.

(Analysis of frequency of gallbladder disease among OCC users and matched controls showed increased risk with OCC use in early years that was later followed by decreased risk, making the overall association questionable; “it is unlikely that all the previous studies were incorrect”).

Helling TS, Wood WG. Oral contraceptives and cancer of the liver: a review with two additional cases. *Am J Gastroenterol.* 1982;77:504–8. PubMed PMID: 6283882.

(21 and 33 year old women on OCCs for 2 and 15 years presented with abdominal pain and found to have hepatocellular carcinoma without cirrhosis, both dying within a year).

Goodman ZD, Ishak KG. Hepatocellular carcinoma in women: probable lack of etiologic association with oral contraceptive steroids. *Hepatology.* 1982;2:440–4. PubMed PMID: 6284630.

(In the published literature, there were 34 reports of hepatocellular carcinoma [HCC] in women on OCCs, but relative risk is unknown; among 128 cases of HCC in women in files of Armed Forces Institute of Pathology between 1953 and 1980, 48 were below 40 years of age, of whom only 27% were on OCCs and 62% of these had fibrolamellar carcinoma, suggesting that the link between HCC with OCC use is due to chance).

Bühler H, Pirovino M, Akobiantz A, Altorfer J, Weitzel M, Maranta E, Schmid M. Regression of liver cell adenoma. A follow-up study of three consecutive patients after discontinuation of oral contraceptive use. *Gastroenterology*. 1982;82:775–82. PubMed PMID: 6277724.

(Found 4 cases of hepatic adenoma in young women between 1975-78, all on OCCs; one resected and three stopped OCCs and were followed, all regressed over 1-3 years).

Shar SR, Kew MC. Oral contraceptives and hepatocellular carcinoma. *Cancer*. 1982;49:407–10. PubMed PMID: 6274509.

(23 year old woman on OCCs for 22 months presented with acute rupture of hepatocellular carcinoma, no other risk factors, dying 2 years later of progressive cancer).

Kolb A. Benign liver tumors and oral contraceptives. *Acta Chir Scand*. 1982;148:89–91. PubMed PMID: 7136416.

(30 year old woman on OCCs for 15 years presented with abdominal mass found to be “orange” sized hepatic adenoma).

Freedman AN. Liver lesions and oral contraceptives. *Can Med Assoc J*. 1982;126:1149–50. PubMed PMID: 7074431.

(32 year old woman presented with pain and multiple cavernous hemangiomas and a focal nodular hyperplasia with resolution after resection and stopping OCCs).

Zafrani ES, von Pinaudeau Y, Dhumeaux D. Drug-induced vascular lesions of the liver. *Arch Intern Med*. 1983;143:495–502. PubMed PMID: 6338851.

(Review of vascular lesions of liver associated with medications including OCCs: Budd Chiari syndrome, veno-occlusive disease, sinusoidal dilatation, peliosis hepatis, and vascular tumors).

Henderson BE, Preston-Martin S, Edmondson HA, Peters RL, Pike MC. Hepatocellular carcinoma and oral contraceptives. *Br J Cancer*. 1983;48:437–40. PubMed PMID: 6311235.

(Search for all deaths from liver cancer in women ages 18-39 in Los Angeles County from 1975-80 found 12 cases; 11 were interviewed and matched with controls; 3 were fibrolamellar; 1 occurred with adenoma and focal nodular hyperplasia; 10 cases had used OCCs and average duration was significantly longer than in controls[~5 vs ~2 years]).

Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PF II. Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. *Gastroenterology*. 1983;84:994–1002. PubMed PMID: 6299876.

(Retrospective analysis of 23 hepatic adenomas and 41 focal nodular hyperplasias (FNH) seen at the Mayo Clinic between 1961-80; 90% in women, mean age 34 years, OCC use in 80-83%; adenomas typically presented with pain and were larger [9 cm], FNH as an incidental finding and smaller [4 cm]; liver enzymes were usually normal; survival excellent; one woman with hepatic adenoma died 2 years later of hepatocellular carcinoma).

Lewis JH, Tice HL, Zimmerman HJ. Budd-Chiari syndrome associated with oral contraceptive steroids: review of treatment of 47 cases. *Dig Dis Sci*. 1983;28:673–83. PubMed PMID: 6872799.

(26 year old woman on OCCs for 7 year presented with 3 month history of fluid retention, edema and ascites which resolved clinically after stopping OCCs and use of aspirin and dipyridamole; review of literature and questionnaires sent to U.S. hepatologists identified 47 cases of Budd-Chiari syndrome associated with OCCs, some requiring surgical intervention: Case 4).

Forman D, Doll R, Peto R. Trends in mortality from carcinoma of the liver and the use of oral contraceptives. *Br J Cancer*. 1983;48:349–54. PubMed PMID: 6615697.

(Analyzed UK national death rates for liver tumors from 1958-81; liver tumors were rare, but there was a slight increase in rate among women ages 20 to 49 years between 1970 and 81; there were several possible explanations for this increase other than OCC use).

Gala KV, Griffin TW. Hepatomas in young women on oral contraceptives: report of two cases and review of the literature. *J Surg Oncol.* 1983;22:11–4. PubMed PMID: 6296542.

(Two cases: 40 year old woman with hepatocellular carcinoma [HCC] had taken OCCs for 8 years, stopping 3 years before presentation, successfully resected; 35 year old woman with metastatic HCC had been on OCCs for 12 years, died on chemotherapy; review of 25 cases in the literature).

Barrows GH, Christopherson WM. Human liver tumors in relation to steroidal usage. *Environ Health Perspect.* 1983;50:201–8. PubMed PMID: 6307679.

(Registry of liver tumors in young women since 1973 had 98 cases of focal nodular hyperplasia, 71 hepatic adenomas and 23 hepatocellular carcinomas; OCC use in >80% of all three groups).

Lieberman DA, Keefe LB, Stenzel P. Severe and prolonged oral contraceptive jaundice. *J Clin Gastroenterol.* 1984;6:145–8. PubMed PMID: 6715853.

(22 year old woman developed jaundice and pruritus after first cycle of OCCs with prolonged cholestatic course [bilirubin rising from ~7.0 to 19.5 mg/dL, ALT 180 to 291 U/L, Alk P ~170 to 556 U/L], requiring 6 months to resolve: Case 2).

Jacobs MB. Hepatic infarction related to oral contraceptive use. *Arch Intern Med.* 1984;144:642–3. PubMed PMID: 6703837.

(30 year old woman cigarette smoker on OCCs for 10 years developed abdominal pain, worsening ALT and Alk P, and was found to have hepatic artery thrombosis and liver infarcts, ultimately resolving after stopping OCCs).

Scragg RK, McMichael AJ, Seamark RF. Oral contraceptives, pregnancy and endogenous oestrogen in gall stone disease: a case-control study. *Br Med J (Clin Res Ed).* 1984;288:1795–99. PubMed PMID: 6428548.

(Case controlled study of 200 hospitalized patients with gallstone disease; increased risk among young women who had taken OCCs, but decreased risk in older woman with a history of OCC use).

Scott LD, Katz AR, Duke JH, Cowan DF, Maklad NF. Oral contraceptives, pregnancy and focal nodular hyperplasia of the liver. *JAMA.* 1984;251:1461–3. PubMed PMID: 6700042.

(36 year old woman on OCCs for 11 years developed hepatic mass which regressed on stopping OCCs, but arose again during a pregnancy; resection showed focal nodular hyperplasia with prominent central scar).

Schmitt FC, Luchsinger AE, Melo CR, Melo IS, Cechella MS. *Arq Gastroenterol.* 1984;20:153–5. [Hepatic cell adenoma and peliosis hepatis in women using oral contraceptives]. PubMed PMID: 6331355.

Mays ET, Christopherson W. Hepatic tumors induced by sex steroids. *Semin Liver Dis.* 1984;4:147–57. PubMed PMID: 6087460.

(Review of experience with 201 benign tumors of liver in women, ages 14 to 57; 98 were diagnosed as focal nodular hyperplasia, 2 adenoma and 23 hepatocellular carcinoma, 9 unclassified; history of OCC use in 82% regardless of histological diagnosis).

Jiménez Garrido MC, Aguinaga Manzanos MV, Miguel Velasco JE, Parada Herrero R, Placer Galan C, Sagredo Ruperez P, Soleto Saez E. *Rev Esp Enferm Apar Dig.* 1984;65:71–5. [Hepatic adenomas and oral contraceptives]. PubMed PMID: 6322251.

(52 year old woman on OCCs for 16 years presented with abdominal pain and laparotomy showed multiple adenomas).

- Bretagne JF, Deugnier Y, Launois B, Gosselin M, Ferrand B, Gastard J. Gastroenterol Clin Biol. 1984;8:768–9. [Regenerative nodular hyperplasia, hepatocellular carcinoma and oral contraceptives]. French. PubMed PMID: 6098506.
- (31 year old on OCCs for 12 years developed hepatic mass that had features of focal nodular hyperplasia with areas of hepatocellular carcinoma with subsequent spread, rise in alpha-fetoprotein and death 9 months later).*
- Terpstra OT, ten Kate FJ, van Urk H. Long-term survival after resection of a hepatocellular carcinoma with lymph node metastasis and discontinuation of oral contraceptives. Am J Gastroenterol. 1984;79:474–8. PubMed PMID: 6328973.
- (21 year old woman on OCCs for 2.5 years was found to have a 10 cm hepatocellular carcinoma that was resected; OCCs were stopped and she remained well during 6 years of follow-up despite the finding of a microscopic lymph node metastases).*
- Hromas RA, Srigley J, Murray JL. Clinical and pathological comparison of young adult women with hepatocellular carcinoma with and without exposure to oral contraceptives. Am J Gastroenterol. 1985;80:479–85. PubMed PMID: 2408465.
- (Retrospective study of 29 young women with hepatocellular carcinoma seen between 1960-85 comparing those with [n=15] and without [n=14] estrogen exposure found minor differences, but suggested more benign course for those related to estrogens).*
- Eugene M, Chong MF, Genin R, Amat D. Mediterr Med. 1985;13:21–4. [Peliosis hepatis and oral contraceptives: a case report]. PubMed PMID: 12281005.
- (29 year old woman presented with abdominal pain and bloating and was found to have ascites and varices; biopsy showed peliosis hepatis).*
- Spormann H, Willgeroth C, Tautenhahn P. Zentralbl Allg Pathol. 1985;130:545–50. [Peliosis hepatis with liver rupture]. PubMed PMID: 3834715.
- (50 year old woman presented with hepatic rupture with massive peliosis and 8 cm tear; no mention of whether she was taking OCCs or estrogens).*
- Dean PJ, Haggitt RC, O'Hara CJ. Malignant epithelioid hemangioendothelioma of the liver in young women. Relationship to oral contraceptive use. Am J Surg Pathol. 1985;9:695–704. PubMed PMID: 3904492.
- (Five cases of epithelioid hemangioendothelioma seen between 1980-83: all women usually presenting with right upper quadrant pain, all had taken OCCs for 4-7 years [up to 8 years before presentation], 3 died during follow up of disease progression).*
- Gonzalez F, Marks C. Hepatic tumors and oral contraceptives: surgical management. J Surg Oncol. 1985;29:193–7. PubMed PMID: 3001424.
- (Retrospective analysis of 14 patients with benign liver tumors [88% adenomas]; 12 women, 11 on OCCs).*
- Flejou JF, Barge J, Menu Y, Degott C, Bismuth H, Potet F, Benhamou JP. Liver adenomatosis: an entity distinct from liver adenoma? Gastroenterology. 1985;89:1132–8. PubMed PMID: 2412930.
- (Between 1979 and 1984, authors saw 5 patients with liver adenomatosis [3 men, 2 women not on OCCs] and 20 with adenoma [18 women, 14 on OCCs] suggesting a separate, possibly genetic, cause for adenomatosis).*
- Gordon SC, Reddy KR, Livingstone AS, Jeffers LJ, Schiff ER. Resolution of a contraceptive-steroid-induced hepatic adenoma with subsequent evolution into hepatocellular carcinoma. Ann Intern Med. 1986;105:547–49. PubMed PMID: 3019201.

(36 year old woman on OCCs for 14 years presented with 13 cm hepatic adenoma which decreased in size and became undetectable 2 years after stopping OCCs; 7 years later during cholecystectomy found to have a 4 cm mass with hepatocellular carcinoma, later metastasizing to peritoneum).

Neuberger J, Forman D, Doll R, Williams R. Oral contraceptives and hepatocellular carcinoma. *Br Med J (Clin Res Ed)*. 1986;292:1355–7. PubMed PMID: 3011185.

(Among 26 women less than 50 years old with hepatocellular carcinoma and with cirrhosis, 18 had used OCCs; compared to a control population relative risk for use of OCCs for more than 8 years was 4.4 in those with liver cancer; no increased risk with shorter durations of use).

Forman D, Vincent TJ, Doll R. Cancer of the liver and the use of oral contraceptives. *Br Med J (Clin Res Ed)*. 1986;292:1357–61. PubMed PMID: 3011186.

(Case control study of 30 women with liver cancer, 19 with hepatocellular carcinoma [HCC] and 11 with cholangiocarcinoma; relative risk for OCCs was 3.8 for HCC [increasing with greater years of use], but 0.3 for OCC use in cholangiocarcinoma).

Iverson O-E, Thoresen SØ. Oral contraceptives and hepatocellular carcinoma. *Br Med J (Clin Res Ed)*. 1986;292:1668.

(Review of national records from Norway demonstrated rise in rates of hepatocellular carcinoma among women, but only in those >45 years, suggesting little effect of introduction of OCCs).

Brosens I, Johanisson E, Baulieu E-E, Benagiano G, Cooke ID, Goldzieher JW, Hammerstein J, et al. Oral contraceptives and hepatocellular carcinoma. *Br Med J (Clin Res Ed)*. 1986;292:1667–8. PubMed PMID: 3013358.

(International Committee for Research in Reproduction comments that studies of Neuberger and Forman still show that hepatocellular carcinoma is very rare and the association with OCCs still unproven).

Valla D, Le MG, Poynard T, Zucman N, Rueff B, Benhamou JP. Risk of hepatic vein thrombosis in relation to the recent use of oral contraceptives: a case control study. *Gastroenterology*. 1986;90:807–11. PubMed PMID: 3949113.

(Case control study of 33 cases of hepatic vein thrombosis and 128 matched controls identified via questionnaires to 25 French Hepatology centers; OCC use in 54% of cases, 31% of controls for odds ratio of 2.37; 72% of OCC related cases had another underlying predisposing condition).

Grigsby P, Meyer JS, Sicard GA, Huggins MB, Lamar DJ, DeSchryver-Kecskemeti K. Hepatic adenoma within a spindle cell carcinoma in a woman with a long history of oral contraceptives. *J Surg Oncol*. 1987;35:173–9. PubMed PMID: 2439848.

(38 year old on OCCs for 8 years presented with a hepatic mass found to be hepatic adenoma within a multicentric anaplastic spindle cell tumor).

Kreitner KF, Thelen M, Schild H, Heintz A, Störkel S. *Dtsch Med Wochenschr*. 1987;112:891–6. [Epidemiological and clinical aspects of focal nodular hyperplasia of the liver. An assessment of 886 cases]. German. PubMed PMID: 3034543.

(Review of literature and 19 local cases of focal nodular hyperplasia; found 886 cases, mostly published in previous 15 years, 82% women, mean age 32 years, 58% on OCCs; 0.3 to 24 cm [mean=6 cm], 35% with symptoms, 20% with palpable mass, prognosis good, rare reports of subsequent malignancy).

Ishak KG, Zimmerman HJ. Hepatotoxic effects of the anabolic/androgenic steroids. *Semin Liver Dis*. 1987;7:230–6. PubMed PMID: 3317860.

(Extensive review of hepatotoxicity of androgenic steroids).

van Erpecum KJ, Janssens AR, Kreuning J, Ruiten DJ, Kroon HM, Grond AJ. Generalized peliosis hepatitis and cirrhosis after long-term use of oral contraceptives. *Am J Gastroenterol.* 1988;83:572–5. PubMed PMID: 3129933.

(43 year old woman with epigastric discomfort and fatigue on OCCs for 12 years had a large liver and abnormal liver scan, [bilirubin 1.0 mg/dL, ALT 21 U/L, Alk P 376 U/L], liver biopsy showing peliosis; OCCs were stopped, but she developed progressive liver disease with high Alk P [1208 U/L] but minimal ALT elevations [45 U/L], ultimately requiring liver transplantation 11 years later).

Heresbach D, Deugnier Y, Brissot P, Bourel M. *Ann Gastroenterol Hepatol (Paris).* 1988;24:189–91. [Sinusoid dilatation and the use of oral contraceptives. Apropos of a case with a review of the literature]. PubMed PMID: 3048199.

(23 year old woman on OCCs for 7 years was admitted for abdominal pain [ALT 149 U/L, Alk P 37 U/L, bilirubin not provided] and liver biopsy showed sinusoidal dilatation without inflammation, necrosis or fibrosis], symptoms and ALT elevations resolving within 8 days of stopping OCCs).

Marks WH, Thompson N, Appleman H. Failure of hepatic adenomas (HCA) to regress after discontinuance of oral contraceptives. An association with focal nodular hyperplasia (FNH) and uterine leiomyoma. *Ann Surg.* 1988;208:190–5. PubMed PMID: 2840865.

(Three cases; 34 to 37 year old women on OCCs for 2-3 years [but 6-10 years before clinical presentation] found to have hepatic adenomas, two also had focal nodular hyperplasia).

Valla D, Benhamou JP. Liver diseases related to oral contraceptives. *Dig Dis.* 1988;6:76–86. PubMed PMID: 2834121.

(Review of hepatic complications of OCCs including intrahepatic cholestasis, adenoma, focal nodular hyperplasia, hepatocellular carcinoma, sinusoidal dilatation, Budd Chiari syndrome and portal vein thrombosis).

Ferrara BE, Rutland ED. Liver tumor in long-term user of oral contraceptives. *Postgrad Med.* 1988;84:107–9. PubMed PMID: 2847128.

(36 year old woman on OCCs for 6 years presented with rupture of 15 x10 cm hepatic adenoma).

Conter RL, Longmire WP Jr. Recurrent hepatic haemangiomas: possible association with estrogen therapy. *Ann Surg.* 1988;207:115–9. PubMed PMID: 2829759.

(4 cases of recurrent giant hepatic hemangiomas [>4 cm]; 3 in women; each with recurrence many years later while on chronic estrogen therapy).

Balázs M. Sinusoidal dilatation of the liver in patients on oral contraceptives. Electron microscopic study of 14 cases. *Exp Pathol.* 1988;35:231–7. PubMed PMID: 3240791.

(Electron microscopic analysis of 14 liver biopsies from 37 women on OCCs for 2-12 years undergoing routine cholecystectomy who were found to have hepatomegaly; enlarged but intact endothelial cells, slight collagen, hepatocytes normal, sinusoids empty and capillarized).

Palmer JR, Rosenberg L, Kaufmann DW, Warshauer NE, Stolley P, Shapiro S. Oral contraceptive use and liver cancer. *Am J Epidemiol.* 1989;130:878–82. PubMed PMID: 2554724.

(Among 9 cases of hepatocellular carcinoma in women 19 to 54 years old who were identified between 1977-85 in five US medical centers, 89% were on OCCs compared to 36% of controls, for relative risk of 20).

Foitt DR, Hyman G, Lefkowitz JH. Jaundice and intrahepatic cholestasis following high-dose megestrol acetate for breast cancer. *Cancer.* 1989;63:438–9. PubMed PMID: 2912522.

(Woman with breast cancer treated with high doses of megestrol [progesterone] developed abnormal liver tests [ALT 160 U/L, Alk P 324 U/L] five weeks later, followed by jaundice [bilirubin rising to 16 mg/dL], dying suddenly a few days later and having multiple metastases in liver).

Gyorffy EJ, Bredfeldt JE, Black WC. Transformation of hepatic cell adenoma to hepatocellular carcinoma due to oral contraceptive use. *Ann Intern Med.* 1989;110:489–90. PubMed PMID: 2537593.

(58 year old on OCCs for 19 years found to have 8 by 12 cm adenoma; stopped OCCs, but 2-3 years later had rising alpha-fetoprotein and biopsy showed hepatocellular carcinoma).

La Vecchia C, Negri E, Parazzini F. Oral contraceptives and primary liver cancer. *Br J Cancer.* 1989;59:460–1. PubMed PMID: 2930715.

(Case control study from Italy identified 21 women [ages 32 to 59 years] with liver cancer diagnosed between 1984-87; only 4 cases [19%] used OCCs compared to 8% of controls; relative risk for OCC use <5 years was 1.8 and for >5 years 8.3; but based on few cases).

Combined oral contraceptives and liver cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer.* 1989;43:254–9. PubMed PMID: 2645220.

(Results of hospital based, case control study of 122 cases of primary liver cancer and 802 matched controls; no increase in risk associated with OCC use, but most cases were from areas of the world with high rates of hepatitis B and most OCC use was for a short duration).

Kew MC, Song E, Mohammed A, Hodgkinson J. Contraceptive steroids as a risk factor for hepatocellular carcinoma: a case/control study in South African black women. *Hepatology.* 1990;11:298–302. PubMed PMID: 2155169.

(Case control study in 46 women, ages 19 to 54 years with hepatocellular carcinoma from an endemic area for hepatitis B; 32% of cases and 37% of controls had used OCCs, whereas 41% of cases versus 9% of controls had HBsAg in serum).

Korula J, Yellin A, Knel G, Camporiofi G, Nichols P. Hepatocellular carcinoma coexisting with hepatic adenoma—Incidental discovery after long-term oral contraceptive use. *West J Med.* 1991;155:416–8. PubMed PMID: 1663298.

(40 year old woman on OCCs for 15 years and estrogens for 6 years found to have an incidental hepatic mass, which on resection was adenoma with areas of hepatocellular carcinoma).

Prentice RL. Epidemiologic data on exogenous hormones and hepatocellular carcinoma and selected other cancers. *Prev Med.* 1991;20:38–46. PubMed PMID: 1848935.

(Review of epidemiologic evidence linking OCCs and exogenous estrogen use to cancers: combing 4 case control studies of hepatocellular carcinoma found relative risk of 2.6 for ever using OCCs, 9.6 for prolonged use).

Adam G, Lesser T, Neumann R. *Zentralbl Chir.* 1991;116:399–403. [Liver rupture in peliosis hepatis]. PubMed PMID: 1907060.

(44 year old woman on OCCs for 13 years developed abdominal pain and anemia leading to diagnosis of hepatic bleeding from peliosis hepatis, with fatal outcome after attempted resection).

Tao LC. Are oral contraceptive-associated liver cell adenomas premalignant? *Acta Cytol.* 1992;36:338–44. PubMed PMID: 1316028.

(Among 1670 patients undergoing fine needle aspiration of diagnosis of liver masses between 1977-90 in Toronto, 99 patients had hepatocellular carcinoma [3 on OCCs] and 9 had hepatic adenoma [all on OCCs]).

Wedén M, Glaumann H, Einarsson K. Protracted cholestasis probably induced by oral contraceptive. *J Intern Med.* 1992;231:561–5. PubMed PMID: 1602295.

(35 year old woman on OCCs for 14 years found to have elevations in Alk P 4 times ULN, but normal bilirubin and ALT; Alk P improved after stopping, but was still elevated 10 years later).

Stanford JL, Thomas DB. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Reproductive factors in the etiology of hepatocellular carcinoma. *Cancer Causes and Control*. 1992;3:37–42. PubMed PMID: 1311212.

(Results from hospital based case control study in 4 developing countries of 83 patients with hepatocellular carcinoma [HCC] vs 596 controls found having multiple full term pregnancies, but not use of OCCs was associated with HCC).

Hsing AW, Hoover RN, McLaughlin JK, CoChien HT, Wacholder S, Blot W, Fraumeni JF Jrl. Oral contraceptives and primary liver cancer among young women. *Cancer Causes Control*. 1992;3:43–8. PubMed PMID: 1536912.

(Analysis of National Mortality Followback Survey, identifying 76 cases of primary liver cancer, 22 bile duct cancers and 629 controls; OCC use in 54% of cases vs 44% of controls, odds ratio of 1.6 for ever use and 2.0 for >10 years of use).

Le Bail B, Jouhanole H, Deugnier Y, Salame G, Pellegrin JL, Saric J, Balabaud C, Bioulac Sage P. Liver adenomatosis with granulomas in two patients on long-term oral contraceptives. *Am J Surg Pathol*. 1992;16:982–7. PubMed PMID: 1357995.

(Two cases of hepatic adenomatosis in women, 39 and 52 years old, on OCCs for 12 and 18 years; one continued to have new lesions during follow up off of OCCs).

Tavani A, Negri E, Parazzini F, Franceschi S, La Vecchia C. Female hormone utilization and risk of hepatocellular carcinoma. *Br J Cancer*. 1993;67:635–7. PubMed PMID: 8382515.

(Case control study of 82 Italian women [ages 28 to 73 years] with diagnosis of hepatocellular carcinoma; relative risk was OCC users was 2.6 and risk increased with duration of use, but overall use was low [21%]).

Thijs C, Leffers P, Knipschild P. Oral contraceptive use and the occurrence of gallstone disease—a case-control study. *Prev Med*. 1993;22:122–31. PubMed PMID: 8475008.

(Case control study of gallstone disease from the Netherlands matched 110 cases with 355 controls for OCC use and duration; after adjusting for many confounders, found a mild early effect of OCC [first 5 years] use that disappeared with time).

Thijs C, Leffers P, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. *Am J Public Health*. 1993;83:1113–20. PubMed PMID: 8342719.

(Metaanalysis identified 25 studies of association of OCC use and gallstone disease; many inconsistencies in conclusions and many confounding factors including latency from development of gallstones and appearance of symptoms and changes in OCC formulations; concluded that OCC use probably had a weak effect, if any at all).

Ferrell LD. Hepatocellular carcinoma arising in a focus of multilobular adenoma. A case report. *Am J Surg Pathol*. 1993;17:525–9. PubMed PMID: 8385884.

(29 year old woman with abdominal pain, hepatic mass and Alk P >2000 U/L, found to have an 18 cm hepatic adenoma within which was a 5 cm hepatocellular carcinoma; patients was without evidence of recurrence 4 years later).

Reyes H, Simon FR. Intrahepatic cholestasis of pregnancy: an estrogen-related disease. *Semin Liver Dis*. 1993;13:289–301. PubMed PMID: 8235718.

(Review of clinical features, epidemiology, pathogenesis and management of intrahepatic cholestasis of pregnancy and its relation to OCCs and estrogens, including effects of ursodiol in improving pruritus, and ALT and bile salt levels).

Lindgren A, Olsson R. Liver damage from low-dose oral contraceptives. *J Intern Med.* 1993;234:287–92. PubMed PMID: 8354979.

(Analysis of adverse drug reaction reports to Swedish Registry for 1965-75 showed marked decrease in reports of liver injury from OCCs during period of lowering estrogen dose in pill; fell to 1 per million OCC cycles).

Chu G, Farrell GC. Portal vein thrombosis associated with prolonged ingestion of oral contraceptive steroids. *J Gastroenterol Hepatol.* 1993;8:390–3. PubMed PMID: 8374097.

(38 year old woman smoker on OCCs for 24 years developed portal vein thrombosis, responding to anticoagulation and stopping OCCs).

Grodstein F, Colditz GA, Hunter DJ, Manson JE, Willett WC, Strampfer MJ. A prospective study of symptomatic gallstones in women: relation with oral contraceptives and other risk factors. *Obstet Gynecol.* 1994;84:207–14. PubMed PMID: 8041531.

(Analysis of Nurses Health Study cohort based upon questionnaires found 425 cases of symptomatic gallstones, showed minimal association with long term OCC use [relative risk 1.5], but strong association with higher body mass index and weight gain; lesser association with smoking and parity).

Rabe T, Feldmann K, Grunwald K, Runnebaum B. Liver tumors in women on oral contraceptives. *Lancet.* 1994;344:1568–9. PubMed PMID: 7983964.

(Since 1971, 637 cases of liver tumors in women on OCCs, but no cases reported with use of cyproterone).

Herman P, Machado MA, Volpe P, et al. *Rev Hosp Clin Fac Med Sao Paulo.* 1994;49:30–3. [Transformation of hepatic adenoma into hepatocellular carcinoma in patients with prolonged use of oral contraceptives]. Portuguese. PubMed PMID: 8029613.

(Two cases of hepatic adenoma with focal areas of hepatocellular carcinoma in 30 and 37 year old women on OCCs for 15 and 20 years).

Gisbert PJ, González A, Moreira V, Sanromán LA, Hernández F, Cano A. *Rev Esp Enferm Dig.* 1994;85:475–7. [An intrahepatic hematoma secondary to peliosis hepatis in a female patient treated with oral contraceptives]. PubMed PMID: 8068426.

(40 year old woman on OCCs for 3 years presented with abdominal pain found to have spontaneous hepatic hematomas due to widespread peliosis).

Colditz GA. Oral contraceptive use and mortality during 12 years of follow-up: the Nurses' Health Study. *Ann Intern Med.* 1994;120:821–6. PubMed PMID: 8154642.

(Analysis of Nurse's Health Study: in 166,755 women found no increase in risk of mortality associated with OCC even after multivariable adjustment).

Mant JWF, Vessey MP. Trends in mortality from primary liver cancer in England and Wales 1975-92: influence of oral contraceptives. *Br J Cancer.* 1995;72:800–3. PubMed PMID: 7669599.

(Age specific mortality trends for primary liver cancer in women remained constant in England and Wales between 1975 and 1992 in all age groups; death rates being ~1.4 per million in women 25 to 34 years old).

Staub PG, Leibowitz CB. Peliosis hepatis associated with oral contraceptive use. *Australas Radiol.* 1996;40:172–4. PubMed PMID: 8687355.

(35 year old on OCCs for several years developed abdominal pain with multiple liver lesions on ultrasound and CT, biopsy showing peliosis, improvement but not resolution on ultrasound 6 months later; no liver test results provided).

- Perret AG, Mosnier JF, Porcheron J, Cuilleron M, Berthoux P, Boucheron S, Audigier JC. Role of oral contraceptives in the growth of a multilobular adenoma associated with a hepatocellular carcinoma in a young woman. *J Hepatol.* 1996;25:976–9. PubMed PMID: 9007729.
- (24 year old woman on OCCs for 3 years presented with abdominal pain and found to have a 14 cm adenoma with focal HCC which was resected).*
- Waetjen LE, Grimes DA. Oral contraceptives and primary liver cancer: temporal trends in three countries. *Obstet Gynecol.* 1996;88:945–9. PubMed PMID: 8942832.
- (Analysis of primary liver cancer deaths from US, Japan and Sweden with several hundred million woman-years of exposures to OCCs found no support for role of OCCs in causing hepatocellular carcinoma).*
- Fiel MI, Min A, Gerber MA, Faire B, Schwartz M, Thung SN. Hepatocellular carcinoma in long-term oral contraceptive use. *Liver.* 1996;16:372–6. PubMed PMID: 9021715.
- (4 women on OCCs for 8-15 years presented with hepatocellular carcinoma with accompanying cirrhosis; two died and two survived long term after resection and stopping OCCs).*
- Persson I, Yuen J, Bergkvist L, Schairer C. Cancer incidence and mortality in women receiving estrogen-replacement therapy—long-term follow-up of a Swedish cohort. *Int J Cancer.* 1996;67:327–32. PubMed PMID: 8707404.
- (Among 22,579 women on estrogen replacement therapy followed for an average of 13.2 years, 2330 cancers occurred, including 14 liver cancers, lower incident rate ratio [0.6] than expected).*
- Benhamou JP. *Gastroenterol Clin Biol.* 1997;21:913–5. [Oral contraceptives and benign tumors of the liver]. PubMed PMID: 9587552.
- (Review of the literature on the association of hepatic adenoma, focal nodular hyperplasia and hepatic angioma with use of birth control pills, with recommendations on management).*
- Hannaford PC, Kay CR, Vessey MP, Painter R, Mant J. Combined oral contraceptives and liver disease. *Contraception.* 1997;55:145–51. PubMed PMID: 9115002.
- (Analysis of two large prospective studies of OCC use from the UK [>200,000 women-years] found low rate of liver disease and no association with OCC use; in one study, a possible increased risk for mild liver disease during first 4 years of use).*
- The Collaborative MILTS Project Team. Oral contraceptives and liver cancer. Results of the Multicentre International Liver Tumor Study (MILTS). *Contraception.* 1997;56(5):275–84. PubMed PMID: 9437555.
- (Case control study among 317 women <65 years old with hepatocellular carcinoma; relative risk among OCC users was 0.75 compared to controls with no increase with longer use; important risk factors were hepatitis B and C; however, after excluding these risk factors, the relative risk was increased for women who used OCCs for >6 years).*
- Heinemann LA, Weimann A, Gerken G, Thiel C, Schlaud M, DoMinh T. Modern oral contraceptive use and benign liver tumors: the German Benign Liver Tumor Case-Control Study. *Eur J Contracept Reprod Health Care.* 1998;3:194–200. PubMed PMID: 10036602.
- (51 hepatic adenomas and 143 focal nodular hyperplasias [FNHs] accrued by 15 medical centers in Germany between 1990-97 and compared to 240 controls; OCC use reported in 94% of adenoma and 96% of FNH cases compared to 70% of controls, but odds ratios were not significant after controlling for age; slight increase in FNH with longer duration of use).*
- Meunier F, Boyer L, Abergel A, Perez N, Ravel A, Lhopital F, Viallet JF. *J Radiol.* 1998;79:341–3. [Regression of a focal nodular hyperplasia after stopping oral contraceptives]. PubMed PMID: 9757261.

- (47 year old woman on OCCs for 7 years found to have 5 cm focal nodular hyperplasia, which persisted for 2 years and then regressed on stopping OCCs and was no longer radiologically evident 5 years later).
- Meissner K. Hemorrhage caused by ruptured liver cell adenoma following long-term oral contraceptives: a case report. *Hepatogastroenterology*. 1998;45:224–5. PubMed PMID: 9496518.
- (41 year old woman on OCCs for 14 years presented with ruptured hepatic adenoma requiring emergency resection).
- Dourakis SP, Tolis G. Sex hormonal preparations and the liver. *Eur J Contracept Reprod Health Care*. 1998;3:7–16. PubMed PMID: 9678067.
- (Review of sex hormones and liver injury; estrogen complications include cholestasis, cholelithiasis, Budd-Chiari syndrome, peliosis, adenomas, focal nodular hyperplasia and HCC).
- Ye MQ, Suriawinata A, Ben Haim M, Parsons R, Schwartz ME. A. 42-year-old woman with liver masses and long-term use of oral contraceptives. *Semin Liver Dis*. 1999;19:339–44. PubMed PMID: 10518313.
- (42 year old woman on OCs for 25 years presented with an abdominal mass which on surgery was found to be 2 adenomas with focal areas of hepatocellular carcinoma, successfully resected).
- Naduka CC. Hepatic adenoma following short period of oral contraceptive use. *J Am Board Fam Pract*. 1999;12:337–9. PubMed PMID: 10477198.
- Makhlouf HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. *Cancer*. 1999;85:562–82. PubMed PMID: 10091730.
- (Analysis of 137 cases of epithelioid hemangioendothelioma from the Armed Forces Institute of Pathology; mean age 47 years, 61% women; incidental finding in 42%, symptoms if present usually pain, ~50% 5-year survival, little information on OCCs, but unlikely to be important).
- De Block CEM, De Leeuw IV, Van Gaal LF. Premenstrual attacks of acute intermittent porphyria: hormonal and metabolic aspects—a case report. *Eur J Endocrinol*. 1999;141:50–4. PubMed PMID: 10407223.
- (38 year old woman with acute intermittent porphyria had several premenstrual attacks resolving with luteinizing hormone-releasing hormone analogue therapy [triptorelin]).
- Follmann M, Heinemann LA, Bauerfeind A, Garbe E. Treatment with potentially hepatotoxic drugs and the risk of hepatocellular carcinoma: results of a European case-control study. *Pharmacoepidemiol Drug Saf*. 2000;9:417–22. PubMed PMID: 19025848.
- (Further analysis of the international case control study of 317 cases of hepatocellular carcinoma and 1060 controls [MILTS], found no association or increase risk of the cancer with common medication use: nitrofurantoin, antidiabetic medications, methyl dopa, clofibrate or immunosuppressive agents).
- Minnema MC, Janssen HL, Niermeijer P, de Man RA. Budd-Chiari syndrome: combination of genetic defects and the use of oral contraceptives leading to hypercoagulability. *J Hepatol*. 2000;33:509–12. PubMed PMID: 11020010.
- (18 year old woman on OCCs for 3 years developed abdominal discomfort and swelling diagnosed as hepatic vein thrombosis and was found to be heterozygous for Factor V Leiden and for Factor II G20210A mutation).
- Mathieu D, Kobeiter H, Maison P, Rahmouni A, Cherqui D, Zafrani ES, Dhumeaux D. Oral contraceptive use and focal nodular hyperplasia of the liver. *Gastroenterology*. 2000;118:560–4. PubMed PMID: 10702207.
- (Analysis of 216 women with focal nodular hyperplasia seen between 1989 and 1998; neither size nor number of masses were associated with OCC use, and neither continued use or pregnancy were associated with tumor).
- Siepmann M, Kirch W. *Dtsch Med Wochenschr*. 2000;125:557–9. [Pruritus during treatment with an estrogen-containing combination]. PubMed PMID: 10835981.

- (51 year old woman developed generalized pruritus while on estrogen-progesterone hormonal replacement therapy for 7 years with normal ALT, Alk P and bilirubin [0.4 mg/dL], unresponsive to antihistamines and steroid creams, resolving rapidly with stopping hormone therapy).*
- Westhoff C, Britton JA, Gammon MD, Wright T, Kelsey JL. Oral contraceptive and benign ovarian tumors. *Am J Epidemiol.* 2000;152:242–6. PubMed PMID: 10933271.
- (In a case control study from 6 New York medical centers, OCC use was associated with a decreased risk of developing benign ovarian tumors).*
- Tajada M, Nerín J, Ruiz MM, Sánchez-Dehesa M, Fabre E. Liver adenoma and focal nodular hyperplasia associated with oral contraceptives. *Eur J Contracept Reprod Health Care.* 2001;6:227–30. PubMed PMID: 11848652.
- (40 year old woman on OCCs for 15 years found to have 8 cm liver mass on incidental ultrasound; stopping OCCs resulted in no change in size and surgery revealed focal nodular hyperplasia).*
- Wang SY, Ruggles S, Vade A, Newman BM, Borge MA. Hepatic rupture caused by peliosis hepatis. *J Pediatr Surg.* 2001;36:1456–9. PubMed PMID: 11528627.
- (3 year old boy with “myotubular myopathy” developed abdominal distension and shock; found to have ruptured hepatic mass, believed to be peliosis hepatis; recovered with surgical and radiologic intervention).*
- Aseni P, Sansalone CV, Sammartino C, Di Benedetto F, Carrafiello G, Giacomoni A, Osio C, et al. Rapid disappearance of hepatic adenoma after contraceptive withdrawal. *J Clin Gastroenterol.* 2001;33:234–6. PubMed PMID: 11500616.
- (25 year old woman on OCCs for 8 years found to have abnormal Alk P and GGT; ultrasound showed 5 cm mass that disappeared 9 months after stopping OCCs).*
- D'Souza RE, Guillebaud J. Risks and benefits of oral contraceptive pills. *Best Pract Res Clin Obstet Gynaecol.* 2002;16:133–54. PubMed PMID: 12041958.
- (Review of risks of OCCs including venous thromboembolism, coronary and cerebrovascular disease and hypertension; breast cancer, liver tumors [3/100,00 users per year], hepatocellular carcinoma [uncertain association] and jaundice [1,10,000 users] but these risks may be lower with current, low dose pills).*
- Scalori A, Tavanni A, Gallus S, La Vecchia C, Colombo M. Oral contraceptives and the risk of focal nodular hyperplasia of the liver: a case-control study. *Am J Obstet Gynecol.* 2002;186:195–7. PubMed PMID: 11854634.
- (Case control study of 23 Italian women with focal nodular hyperplasia; 83% of cases and 59% controls reported OCC use; odds ratio was 2.5, and 4.5 for >3 years of use).*
- Andersson C, Innala E, Backstrom T. Acute intermittent porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. *J Intern Med.* 2003;254:176–83. PubMed PMID: 12859699.
- (Female sex hormones appear to increase porphyrin precursors and may precipitate attacks of acute intermittent porphyria [AIP]; questionnaires completed by 166 women with AIP in Sweden; 91 had symptomatic disease; mean age of onset 25 years and reduction in symptoms after menopause in 50%; pregnancy appeared to have little effect and only 25% reported precipitation of attacks with OCCs; hormonal replacement therapy had no effect).*
- Ito M, Sasaki M, Wen CY, Nakashima M, Ueki T, Ishibashi H, Yano M, et al. Liver cell adenoma with malignant transformation: a case report. *World J Gastroenterol.* 2003;9:2379–81. PubMed PMID: 14562419.
- (57 year old found to have adenoma with area of hepatocellular carcinoma; only OCC use was for one month 27 years previously).*

- Mansvelt B, Etienne PY, Bertrand C, Henrion J, Gerard R. Hepatocellular carcinoma associated with precocious puberty and oral contraceptives. A case report. *Acta Chir Belg.* 2003;103:412–3. PubMed PMID: 14524163.
(36 year old woman on OCCs for 18 years presented with sudden onset of abdominal pain and was found to have well differentiated hepatocellular carcinoma in a liver without fibrosis; resected and was alive without recurrence 4 years later).
- Gemer O, Moscovici O, Ben-Horin CL, et al. Oral contraceptives and liver hemangioma: a case-control study. *Acta Obstet Gynecol Scand.* 2004;83:1199–201. PubMed PMID: 15548156.
(Case control study of 40 women with liver hemangiomas and 109 controls; OCC use in 30% vs 27%).
- Hung NR, Chantrain L, Dechambre S. Peliosis hepatis revealed by biliary colic in a patient with oral contraceptive use. *Acta Chir Belg.* 2004;104:727–9. PubMed PMID: 15663284.
(42 year old woman on OCCs for several years developed right upper quadrant pain and tenderness with normal liver tests and multiple cysts and lesions on ultrasound and magnetic resonance [possible peliosis hepatis], decreasing after stopping OCCs).
- Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. *Gastroenterology.* 2004;127(5 Suppl 1):S72–8. PubMed PMID: 15508106.
(Review of risk factors for hepatocellular carcinoma; highest risk with hepatitis B and C [odds ratios 20-24], but also aflatoxin exposure and alcohol use; 8 case control studies in young, non-cirrhotic women for role of OCCs, summary odds ratio of 2.5 for ever using OCCs and 5.8 for longest duration of use; this effect is hard to show in high endemic areas).
- Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. *Arch Intern Med.* 2004;164:1965–76. PubMed PMID: 15477430.
(Systematic review of risk of thromboembolic disease with oral contraceptive use; risk of venous thromboses appears to be increased during the first 6-12 months of therapy, is higher in older women, is higher with higher doses of estrogens, in patients with inherited hypercoagulable states [99 fold with factor V Leiden and 16-fold with the prothrombin G20210A mutation]; similar increase in risk [~ 2.1] was also found for hormonal replacement therapy in the Women's Health Initiative).
- Zucman-Rossi J. Genetic alterations in hepatocellular adenomas: recent findings and new challenges. *J Hepatol.* 2004;40:1036–9. PubMed PMID: 15158349.
(Review of role of HNF1 α mutations in adenomatosis; high rate of double, inactivating, somatic mutations in HNF1 α in adenomas linked to birth control pills).
- Hashimoto L, Dabbs A, Sewell P, Doherty M. Resection and radiofrequency ablation of multiple liver adenomas secondary to anti-conceptive pills. *Hepatogastroenterology.* 2004;51:837–8. PubMed PMID: 15143929.
(25 year old woman on OCCs presented with multiple hepatic adenomas, some resected and some treated with radiofrequency ablation).
- Anand V, Gorard DA. Norethisterone-induced cholestasis. *QJM.* 2005;98:232–4. PubMed PMID: 15728406.
(Two cases of cholestatic liver injury in women receiving progesterone contraceptive only; 18 and 34 year old woman with onset of jaundice 2 weeks and 4 years after starting norethisterone [initial bilirubin 2.5 and 1.9 mg/L, ALT 540 and AST 179, Alk P 102 and 532 U/L], resolving within 2-4 months of stopping).
- Lam CM, Yong JL, Chan AO, Ng KK, Poon RT, Liu CL, Lo CM, et al. Better survival in female patients with hepatocellular carcinoma: oral contraceptive pills related? *J Clin Gastroenterol.* 2005;39:533–9. PubMed PMID: 15942442.

(In multivariate analysis of determinants of survival among 3,171 patients with hepatocellular carcinoma, female sex, fewer tumor nodules, smaller size, no vascular or other organ invasion and lack rupture were associated with survival).

Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, Larson JC. Effect of estrogen therapy on gallbladder disease. *JAMA*. 2005;293:330–9. PubMed PMID: 15657326.

(Analysis of Women's Health Initiative postmenopausal hormone trial; among 22,579 women, higher rate of gallbladder events in women who received estrogens, separating after one year with hazard ratio of 1.8; progesterone did not appear to increase the rate further).

Maréchal R, Taccone FS, Bourgeois N, Hittélet A. *Rev Med Brux*. 2005;26:451–4. [Spontaneous intrahepatic haemorrhage due to peliosis hepatis]. PubMed PMID: 16318099.

Ruiz López D, Sánchez Salvador J, Fernández Martín C, Antón Díaz E. *Aten Primaria*. 2005;35:109–10. [Hepatic adenoma related to oral contraceptives use]. PubMed PMID: 15727756.

Giannitrapani L, Soresi M, La Spada E, Cervello M, D'Alessandro N, Montalto G. Sex hormones and risk of liver tumor. *Ann N Y Acad Sci*. 2006;1089:228–36. PubMed PMID: 17261770.

(Review of relationship of androgen and estrogen use and liver tumors. Hemangiomas occur more commonly in women [5:1] as does focal nodular hyperplasia [8:1] but their link to estrogens is controversial; adenomas are clearly linked to estrogen use and are rare in men; hepatocellular carcinoma is more common in men than women [9:1 in some studies] and estrogens appear to increase the risk slightly with an odds ratio of 2.5 for any use and 5.8 for long term use).

La Vecchia C, Tavani A. Female hormones and benign liver tumours. *Dig Liver Dis*. 2006;38:535–6. PubMed PMID: 16753350.

(Review of literature linking estrogen use and hepatic adenomas, focal nodular hyperplasia and hemangiomas).

Maheshwari S, Sarraj A, Kramer J, El-Serag HB. Oral contraception and the risk of hepatocellular carcinoma. *J Hepatol*. 2007;47:506–13. PubMed PMID: 17462781.

(Metaanalysis of studies on OCCs and hepatocellular carcinoma; 12 case control studies, pooled estimate of odds ratio of 1.57, but overall the evidence "is inconclusive").

Gutiérrez Santiago M, García Ibarbia C, Nan DN, Hernández JL. *Rev Clin Esp*. 2007;207:257–8. [Hepatic lesions and prolonged use of oral contraceptive]. PubMed PMID: 17504674.

(45 year old woman on OCCs for 9 years found to have multiple lesions in the liver due to peliosis, with partial resolution on stopping OCCs).

Dunn JM, McNair A. Prolonged cholestasis following successful removal of common bile duct stones: beware patients on estrogen therapy. *World J Gastroenterol*. 2007;13:6277–80. PubMed PMID: 18069774.

(Two women with prolonged cholestasis after successful removal of common duct stones by ERCP, perhaps exacerbated by OCCs or hormonal replacement therapy).

Proctor DD, Henderson KJ, Dziura JD, White RI Jr. Hormonal therapy for the treatment of gastrointestinal bleeding in hereditary hemorrhagic telangiectasia. *J Clin Gastroenterol*. 2008;42:756–7. PubMed PMID: 18496387.

(Case report of 51 year old woman with hereditary hemorrhagic telangiectasia [HHT] requiring multiple blood transfusions and iron because of gastrointestinal bleeding, had marked decrease in transfusion requirements within 4 months of starting OCCs).

Hay JE. Liver disease in pregnancy. *Hepatology*. 2008;47:1067–76. PubMed PMID: 18265410.

(Review of pregnancy related liver disease including intrahepatic cholestasis of pregnancy defined by pruritus and elevated bile acid levels arising in second half of pregnancy, 25% with jaundice, resolving with delivery, typically recurring with subsequent pregnancies; 15% of cases linked to ABC B4 mutations; treatment includes ursodiol).

Bioulac-Sage P, Laumonier H, Laurent C, Zucman-Rossi J, Balabaud C. Hepatocellular adenoma: what is new in 2008. *Hepatol Int.* 2008;2:316–21. PubMed PMID: 19669260.

(Several gene mutations have been associated with hepatic adenomas some of which have distinct clinical phenotypes; [1] mutations in hepatocyte nuclear factor [HNF] 1 α are found in 35% of adenomas, usually with steatosis and little inflammation; [2] β catenin gene mutations occur in 10% of adenomas and are associated with cytological abnormalities, without steatosis and with a higher rate of malignant transformation; [3] inflammatory adenomas are associated with increases in C-reactive protein in 40-50% of cases; [4] others, ~10% of cases; germline HNF1 α mutations are associated with multiple liver adenomatosis and early onset type 2 diabetes [MODY3]).

Perarnau JM, Bacq Y. Hepatic vascular involvement related to pregnancy, oral contraceptives, and estrogen replacement therapy. *Semin Liver Dis.* 2008;28:315–27. PubMed PMID: 18814084.

(Review of vascular diseases of the liver and role of pregnancy, oral contraceptives and hormonal replacement therapy).

Meier Y, Zodan T, Lang C, Zimmermann R, Kulla K, Ublick GA, Meier PJ, et al. Increased susceptibility for intrahepatic cholestasis of pregnancy and contraceptive-induced cholestasis in carriers of the 1331T>C polymorphism in the bile salt export pump. *World J Gastroenterol.* 2008;14:38–45. PubMed PMID: 18176959.

(21 women with pregnancy- and 4 with OCC-associated cholestasis were assessed for variants in BSEP [ABC B11], MDR3 [ABC B4] and MRP2 [ABC C2]; no specific mutations were found in ABC C2 or B4, but all OCC related cases were homozygous for a single polymorphism in ABC B11, vs 57% of pregnancy-associated and 20% of controls).

Chalasan N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology.* 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 2 cases were attributed to an estrogen containing preparation).

Kapp N, Tilley IB, Curtis KM. The effects of hormonal contraceptive use among women with viral hepatitis or cirrhosis of the liver: a systematic review. *Contraception.* 2009;80:381–6. PubMed PMID: 19751861.

(Scant data are available, but most suggests that OCCs have little effect on the course and outcome of either acute or chronic viral hepatitis).

Bacq Y, Gendrot C, Perrotin F, Lefrou L, Chretien S, Vie-Buret V, Brechot MC, et al. ABCB4 gene mutations and single-nucleotide polymorphisms in women with intrahepatic cholestasis of pregnancy. *J Med Genet.* 2009;46:711–5. PubMed PMID: 19584064.

(Analysis of ABC B4 [flippase: MDR3] sequences in 50 women with intrahepatic cholestasis of pregnancy; 16% had gene mutations, but no distinguishing clinical features between those with and without ABC B4 mutations).

Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. *World J Gastroenterol.* 2009;15:2049–66. PubMed PMID: 19418576.

(Intrahepatic cholestasis of pregnancy occurs worldwide [~1% of pregnancies], but is most common in Chile [1.5-4%] and Scandinavia; higher rates in twin pregnancies and in winter months, and familial associations with gallstones; arises usually in third trimester and resolves within 2 days of delivery; jaundice in 10-15% but

rarely severe; ALT elevated 2-10 fold but not always; Alk P is elevated in normal pregnancy; bile acids invariably elevated; genomic studies suggest enormous heterogeneity; proportion linked to ABC B4 and ABC B11).

Rebouissou S, Amessou M, Couchy G, Poussin K, Imbeaud S, Pilati C, Izard T, Balabaud C, Bioulac-Sage P, Zucman-Rossi J. Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours. *Nature*. 2009;457(7226):200–4. PubMed PMID: 19020503.

(A subset of hepatic adenomas have an inflammatory phenotype and were found to have elevations in acute phase reactants which led to identification of somatic deletions in gp130, a receptor in the IL6 signaling pathway and mutations activated STAT3 and downstream acute phase inflammatory genes).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. *Br J Clin Pharmacol*. 2010;70:721–8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, ethinylestradiol with levonorgestrel accounted for 43 cases [ranking 27th], with an adjusted odds ratio of 1.9 compared to controls).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol*. 2010;105:2396–404. PubMed PMID: 20648003.

(Among 313 cases of drug induced liver injury seen between 1997 and 2008 at a large hospital in Bangalore, India, 1 case was attributed to an OCC).

Elouni B, Ben Salem C, Zamy M, Ganne N, Beaugrand M, Bouraoui K, Biour M. Cytolytic hepatitis possibly related to levonorgestrel/ethinylestradiol oral contraceptive use: 2 case reports. *Ann Pharmacother*. 2010;44:2035–7. PubMed PMID: 21119102.

(Two women, ages 28 and 29, developed marked ALT elevations with no jaundice or Alk P elevations 11 and 8 months after starting OCCs, ALT levels increasing [from 7 to 31 times ULN and from 2 to 23 times ULN] as long as OCCs were continued and resolving within 3-4 weeks once stopped).

Tornai I. *Orv Hetil*. 2010;151:1132–6. [Role of environmental factors in the etiology of hepatocellular carcinoma]. PubMed PMID: 20570793.

(Review of risk factors for hepatocellular carcinoma mentions that OCCs may play a role in some cases).

Jaffar R, Pechet L, Whalen GF, Banner BF. Spontaneous hepatic hemorrhage secondary to prolonged use of oral contraceptives. *Pathol Res Pract*. 2010;206:318–21. PubMed PMID: 19577854.

(45 year old woman who had taken OCCs for 18 years suffered a spontaneous subcapsular hematoma not related to tumor, peliosis or known trauma).

Pauli-Magnus C, Meier PJ, Stieger B. Genetic determinants of drug-induced cholestasis and intrahepatic cholestasis of pregnancy. *Semin Liver Dis*. 2010;30:147–59. PubMed PMID: 20422497.

(Review of pathogenesis of cholestatic liver disorders including intrahepatic cholestasis of pregnancy, which has been linked to genetic variants in the bile salt exporter protein [BSEP, ABC B11]).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology*. 2013;144:1419–25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none of the 96 were attributed to estrogens or OCCs).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino RA, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. *Ann Hepatol.* 2014;13:231–9. PubMed PMID: 24552865.

(Summary of 176 published cases of drug induced liver injury from 9 South American countries implicated a total of 53 drugs, 4 cases being due to estrogens, progestins or birth control pills, all of which were from Chile).

Chalasanani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology* 2015; 148: 1340-52. e7.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 6 [0.7%] were attributed to estrogens or OCCs, all female, ages 16 to 55 years [median 22], onset after 13-70 days [median 27], bilirubin 0.7-12.4 mg/dL, ALT 66-520 U/L, Alk P 54-241, 5 with itching, 3 with jaundice, mild-to-moderate in severity, resolving in all, 4 highly likely and 2 probable).

Loulergue P, Coriat R, Mir O. Recurrent transaminitis induced by oral contraceptives during HIV infection. *Ann Pharmacother.* 2015;49:258–9. PubMed PMID: 25583940.

(45 year old HIV positive woman on long term antiretroviral therapy developed abnormal liver tests without symptoms one month after starting oral contraceptives of ethinyl estradiol and levonorgestrel [bilirubin normal, ALT 17 times ULN], resolving within 3 weeks of stopping and then recurring several years later within 2 weeks of restarting ethinyl estradiol with norgestrel [ALT 12 times ULN], again resolving rapidly upon stopping).

Bourgeois AL, Auriche P, Palmaro A, Montastruc JL, Bagheri H. Risk of hormone therapy in transgender people: Literature review and data from the French Database of Pharmacovigilance. *Ann Endocrinol (Paris).* 2016;77:14–21. PubMed PMID: 26830952.

(Review of the literature and adverse event registries on medical regimens for transgender individuals, trans-females receiving antiandrogens, GnRH and estrogens which can be associated with serum enzyme elevations but has not been linked to clinically apparent liver injury in transgender women).

Choudhary NS, Bodh V, Chaudhari S, Saraf N, Saigal S. Norethisterone related drug induced liver injury: a series of 3 cases. *J Clin Exp Hepatol.* 2017;7:266–8. PubMed PMID: 28970715.

(3 women, ages 27, 43 and 52 with uterine fibroids and vaginal bleeding were treated with norethisterone [5-15 mg daily] for 3-8 weeks when they were found to have abnormal liver tests [bilirubin 0.2-1.0 mg/dL, ALT 614-1058 U/L, Alk P 89-151 U/L], improving within days of stopping the progestin).

Stannov SU, Ries A, Bang UC. Hepatotoxicity induced by a second-generation combined oral contraceptive: case report and review of the literature. *Eur J Contracept Reprod Health Care.* 2019;24:322–4. PubMed PMID: 30983430.

(24 year old woman was found to have ALT elevations without jaundice 4 months after starting oral contraceptives [20 mg ethinyl estradiol and 150 µg levonorgestrel] which rose from 156 to 675 U/L until the OCC were stopped, but then arose anew within 2 weeks of restarting [ALT rising from 15 to 109 U/L], again resolving rapidly upon stopping).

Jetter A, Kullak-Ublick GA. Drugs and hepatic transporters: A review. *Pharmacol Res.* 2020;154:104234. PubMed PMID: 31004787.

(Review of the effects of medications on hepatic transporters, mentions that estrogens are substrates for MRP2 which transport them out of the hepatocyte into the canaliculus).