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**NLM Citation:** LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Gonadotropins. [Updated 2018 Mar 26].
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/

# Gonadotropins

Updated: March 26, 2018.

# OVERVIEW

## Introduction

The gonadotropins are peptide hormones that regulate ovarian and testicular function and are essential for normal growth, sexual development and reproduction. The human gonadotropins include follicle stimulating hormone (FSH) and luteinizing hormone (LH) which are made in the pituitary, and chorionic gonadotropin (hCG) which is made by the placenta. All three gonadotropins are heterodimeric proteins that consist of two peptide chains, the alpha chain is similar in all three, whereas the beta chain is unique and determines the fine receptor specificity and function of each hormone. The pituitary gonadotropins are under the control of gonadotropin releasing hormone (GnRH), a decapeptide produced in the hypothalamus and released in response to circulating levels of estrogens and progesterone. Highly purified and recombinant formulations of the gonadotropins have been developed and used in the treatment of hypogonadism and infertility. Synthetic forms of GnRH have been used with the gonadotropins in assisted reproductive techniques and in vitro fertilization. Therapeutic use of the gonadotropins and GnRH has not been linked to serum enzyme elevations or with clinically apparent liver injury. However, in high doses, the gonadotropins can induce the ovarian hyperstimulation syndrome (OHSS) which may be accompanied by liver test abnormalities, jaundice, edema and ascites.

**Follicle stimulating hormone** (FSH) is a pituitary hormone that regulates growth, sexual development and reproduction, including menstruation, follicular development and ovulation. FSH is regulated, at least in part, by GnRH produced in the hypothalamus in response to multiple signals including circulating levels of sex hormones. FSH interacts with receptors on ovarian follicles and is the major survival factor for the maturing follicles. A surge in FSH levels occurs in the middle of the menstrual cycle leading to ovulation. In men, FSH promotes spermatogenesis and androgen responsiveness in the testes. Thus, FSH is essential for sexual maturation and reproduction in both men and women. Partially and highly purified urinary derived FSH (menotropins, Menopur which also has LH activity; urofollitropin, Bravelle) and recombinant forms of FSH (follitropin alpha, Follistim, Gonal F) are available and approved for use in treatment of infertility and hypogonadism. They are generally given by subcutaneous injection daily or several times weekly. The dose and appropriate regimen vary by indication. These agents should be used only by health care workers with expertise in management of infertility and hypogonadism.

**Luteinizing hormone** (LH) is a pituitary hormone that is essential for sexual development and reproduction in both men and women. LH is regulated by GnRH from the hypothalamus which is sensitive to circulating levels of sex hormones. LH interacts with receptors on ovarian follicles and promotes their maturation. In the middle of the menstrual cycle, a surge of LH triggers ovulation and production of progesterone by the corpus luteum that is necessary for the maturation of the uterine endometrium for implantation of the fertilized egg. In males,

LH stimulates production of testosterone by the testes. LH is used clinically in assisted reproduction techniques (ART) and in vitro fertilization (IVF) to stimulate ovarian follicle maturation. Both urinary derived (menotropin, Menopur, which also has FSH activity) and recombinant forms (lutropin alfa: Luveris) of human LH have been developed, but not all are available in the United States. LH is generally administered by subcutaneous injection in a cyclic and step-wise fashion. The dosages and regimens of administration vary by indication. These agents should be used only by health care workers with expertise in management of infertility and hypogonadism.

**Human chorionic gonadotropin** (kor" ee on' ik) (hCG) is a polypeptide hormone produced by the placenta following implantation of the fertilized egg. Circulating human chorionic gonadotropin interacts with the luteinizing hormone receptors of the ovary, promoting the corpus luteum and its production of progesterone which is necessary to maintain pregnancy and support the growth of the fetus. Injections of hCG mimic the surge in LH that is necessary for ovulation and are used in the therapy of female infertility, in assisted reproduction techniques. In clinical trials, hCG resulted in pregnancies in approximately 30% of women. hCG prepared from urine of pregnant women and was approved for use in the United States in 1967 as treatment of ovulatory dysfunction in women desiring pregnancy. Subsequently, recombinant forms of hCG have been developed and licensed for use. Currently, hCG is available as a powder or in solution generically and under trade names such as Novarel and Pregnyl. Recombinant hCG is available as Overle. The dose and regimen of hCG therapy varies by indication and it should be used only by physicians with expertise in the management of infertility and hypogonadism. Common side effects include headache, nausea, anorexia, and local injection reactions. Uncommon, but potentially severe adverse events include ovarian hyperstimulation syndrome.

**Gonadotropin releasing hormone** (GnRH) is a decapeptide, neurohormone produced in the hypothalamus and released in a pulsatile manner. GnRH acts on the pituitary leading to synthesis and secretion of LH and FSH. GnRH activity is low during childhood and increases markedly during puberty. The proper pulsatile activity of GnRH is necessary for reproduction, but once pregnancy is established it is no longer necessary, gonadotropin activity being assumed by chorionic gonadotropin produced by the placenta. Synthetic GnRH is used as a part of assisted reproductive techniques as a means of controlling ovarian overstimulation. GnRH is available in solution for injection and its use should be restricted to physicians with expertise in assisted reproductive techniques. In addition, several synthetic GnRH analogues and GnRH antagonists have been developed as therapy of various conditions including hormone-sensitive cancers (breast and prostate), endometriosis and precocious puberty. These products are discussed separately in LiverTox as gonadotropin releasing hormone agonists and antagonists.

## Hepatotoxicity

The gonadotropic hormones are usually given in low doses for a short time only and there is little evidence or reason to suspect that they may be hepatotoxic. Injections of LH, FSH, hCG and GnRH, either in short courses or as single injections in assisted reproductive techniques and to stimulate ovulation, have not been linked convincingly to instances of serum enzyme elevations. Even use of more prolonged courses of the gonadotropins for hypogonadism has also not been associated with serum enzyme elevations or other evidence of liver injury. Furthermore, no instances of idiosyncratic, clinically apparent liver injury have been attributed to use of the gonadotropins, alone or in combination.

When used in women for the treatment of infertility, however, the gonadotropins can lead to the ovarian hyperstimulation syndrome (OHSS), severe forms of which can be accompanied by serum enzyme elevations, jaundice and even ascites. This syndrome typically arises within 4 to 14 days of ovarian stimulation with gonadotropins or clomiphene and is characterized by the onset of abdominal pain and distension with ascites and enlarged ovaries and ovarian cysts. There can be marked fluid shifts with hemoconcentration and rapid onset of severe ascites and pleural effusions. Liver tests are elevated in 25% to 40% of patients with OHSS, typically with mild-to-moderate increases in ALT and AST values, but minimal or no elevations in serum

bilirubin and alkaline phosphatase levels. The liver test abnormalities resolve with resolution of the OHSS usually within 2 to 3 weeks of onset. In severe instances, OHSS can be fatal, but death is usually due to dehydration, shock and septicemia rather than hepatic failure. In typical cases with abnormal liver enzymes, liver histology reveals nonspecific changes of sinusoidal dilatation, mild fat accumulation and focal inflammatory infiltrates with macrophages and lymphocytes. OHSS is less common with clomiphene than with human chorionic gonadotropin (hCG) induction of ovulation and appears to be more common with the use of FSH and LH. The liver injury that accompanies OHSS is not due to the gonadotropins per se, but rather secondary to their effects on target organs.

Likelihood score [hCG, FSH, LD, GnRH): E (unlikely causes of clinically apparent liver injury but may precipitate evidence of liver injury as a part of the OHSS).

## Mechanism of Injury

A mechanism of injury that might lead to serum enzyme elevations during gonadotropin therapy is not known. The gonadotropins are peptide hormones and are usually metabolized by the cell on which they act. The liver test abnormalities found during OHSS may be due to fluid shifts, hypovolemia and ischemia.

## Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) during gonadotropin therapy should lead to dose reduction or temporary cessation. The gonadotropins and gonadotropin releasing hormone have not been implicated in cases of severe hepatitis, acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There is no reason to suspect any degree of cross sensitivity in risk for hepatic injury among the various gonadotropins and other agents used to treat infertility.

Drug Class: Obstetrical and Gynecological Agents, Infertility Agents

# CASE REPORT

## Case 1. Jaundice and liver injury during severe ovarian hyperstimulation syndrome.

[Modified from: Obrzut B, Kuczy.ski W, Grygoruk C, Putowski L, Kluz S, Skret A. Liver dysfunction in severe ovarian hyperstimulation syndrome. Gynecol Endocrinol 2005; 21: 45-9. PubMed Citation.]

A 32 year old woman with infertility received a cycle of every other day FSH injections followed by a single infusion of hCG for ovulation induction in preparation for natural insemination and presented several days later with nausea, vomiting, abdominal distention and shortness of breath. On examination, she had tachycardia (110/min) and blood pressure was 100/70 mm Hg. She was pale, diaphoretic and had diffuse tenderness and swelling of the abdomen. Laboratory testing suggested hemoconcentration (hematocrit 51%) and hypoproteinemia (total protein 4.8 g/dL). Ultrasonography demonstrated enlarged ovaries with multilocular cysts (14-18 cm), with mild ascites. She received fluids and albumin infusions, but worsened over the next several days, developed jaundice and worsening ascites (Table). A pleural effusion was present on chest X-ray. She underwent repeated paracenteses and was treated with fluids, antibiotics, corticosteroids and heparin. She gradually improved and was discharged after 7 weeks in the hospital. In follow up, she had an uncomplicated pregnancy and delivered a normal child at 38 weeks gestation.

### Key Points

| | |
|---|---|
| Medication: | Follicle stimulating hormone and human chorionic gonadotropin injections |
| Pattern: | Hepatocellular (R=~50) |

*Table continued from previous page.*

| | |
|---|---|
| Severity: | 4+ (jaundice, hospitalization, ascites, intensive care support) |
| Latency: | Unclear |
| Recovery: | Complete within 2-3 months |
| Other medications: | None mentioned |

## Laboratory Values

| Hospital Day | ALT* (U/L) | Alk P (U/L) | Bilirubin* (mg/dL) | Comments |
|---|---|---|---|---|
| Ovulation induction with FSH and hCG injections | | | | |
| Day 1 | 50 | | 5.0 | Ovarian cysts |
| Day 3 | 450 | | 2.8 | Worsening ascites |
| Day 5 | 1050 | | 3.3 | Transfer to ICU care |
| Day 7 | 2500 | | 1.4 | |
| Day 10 | 3372 | 310 | 3.5 | Peak values |
| Day 13 | 2100 | | 2.8 | |
| Day 21 | 2650 | | 1.5 | |
| Day 25 | 1800 | | 0.8 | |
| Day 31 | 1200 | | 0.8 | |
| Day 42 | 40 | | 0.4 | |
| 8 months | Normal | Normal | Normal | Normal delivery |
| **Normal Values** | **<40** | **<250** | **<1.2** | |

* Values estimated from Figure 1, normal values imputed.

## Comment

The gonadotropins do not seem to be intrinsically hepatotoxic, but they can induce the ovarian hypersensitivity syndrome, severe forms of which may be accompanied by hepatic injury. The pattern of injury is usually a mild jaundice with mild-to-moderate serum enzyme elevations accompanying severe hypoproteinemia and ascites. Recovery usually requires 1 to 4 weeks and follows the resolution of the hyperestrogenism and ovarian hyperstimulation. In this case, there were marked serum aminotransferase elevations with moderate increases in alkaline phosphatase levels, suggesting an element of hypovolemic shock and hepatic ischemic injury. Serial INR, albumin and platelet count results were not provided. The patient ultimately recovered and delivered a "viable" infant after 38 weeks of gestation.

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Follicle Stimulating Hormone – Bravelle®

Luteinizing Hormone – Menopur®

Human Chorionic Gonadotropin – Generic, Novarel® Pregnyl®

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Gonadotropin Releasing Hormone – Generic

**DRUG CLASS**

Infertility Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULAS AND STRUCTURES

| DRUG | CAS REGISTRY NO | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Follicle Stimulating Hormone | 9002-68-0 | Protein | Not Available |
| Luteinizing Hormone | 9002-67-9 | Protein | Not Available |
| Human Chorionic Gonadotropin | 9002-61-3 | Protein | Not Available |
| Gonadotropin Releasing Hormone | 33515-09-2 | Protein | Not Available |

## ANNOTATED BIBLIOGRAPHY

References updated: 26 March 2018

Abbreviations: OHSS, ovarian hyperstimulation syndrome; FSH, follicle stimulating hormone; LH, luteinizing hormone; GnRH, gonadotrophin releasing hormone; hCG, human chorionic gonadotrophin.

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.

*(Review of hepatotoxicity published in 1999; the gonadotropins are not specifically mentioned).*

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

*(Textbook on hepatotoxicity; gonadotropins and fertility agents are not discussed).*

Levin ER, Vitek WS, Hammes SR. Estrogens, Progestins, and the Female Reproductive Tract. 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).*

Lunenfeld B, Blankstein J, Kotev-Emeth S, Kokia E, Geier A. Drugs used in ovulation induction. Safety of patient and offspring. Hum Reprod 1986; 1: 435-9. PubMed PMID: 3106402.

*(Review of safety of clomiphene and human chorionic gonadotropin used as therapy of infertility in women to induce ovulation; no mention of ALT elevations or hepatotoxicity).*

Younis JS, Zeevi D, Rabinowitz R, Laufer N, Schenker JG. Transient liver function tests abnormalities in ovarian hyperstimulation syndrome. Fertil Steril 1988; 50: 176-8. PubMed PMID: 3384112.

*(2 women, ages 24 and 28 years, developed abdominal pain and distension, nausea and dyspnea 7 and 16 days after aspiration of oocytes and therapy with human chorionic gonadotropin [bilirubin 0.7 and 0.8 mg/dL, ALT 103 and 124 U/L, Alk P 94 and 115 U/L, albumin 2.0 and 3.3 g/dL], resolving with resolution of the ascites and ovarian enlargement within 3-4 weeks).*

Sueldo CE, Price HM, Bachenberg K, Steinleitner A, Gitlin N, Swanson J. Liver dysfunction in ovarian hyperstimulation syndrome. A case report. J Reprod Med 1988; 33: 387-90. PubMed PMID: 3130483.

*(29 year old woman with infertility developed ascites and OHSS within a week of stopping a course of human menopausal gonadotropin [bilirubin 2.8 mg/dL, ALT 207 rising to 880 U/L, Alk P 111 U/L], liver biopsy was largely normal except for intramitochondrial paracrystaliine inclusions).*

Metrodin and other drugs that induce ovulation. Med Lett Drugs Ther 1988; 30 (775): 91-2. PubMed PMID: 3137426.

*(Concise review of safety and efficacy of drugs used to induce ovulation, including clomiphene and gonadotropins [including urofollitropin]; no mention of ALT elevations or hepatotoxicity, side effects including multiple pregnancies with all agents and OHSS with gonadotropins).*

Gonadorelin for induction of ovulation. Med Lett Drugs Ther 1990; 32 (823): 70-1. PubMed PMID: 2196417.

*(Gonadorelin is a synthetic gonadotropin releasing factor approved for use in treatment of amenorrhea and to induce ovulation, side effects being multiple pregnancies, hypersensitivity reactions and OHSS; no mention of ALT elevations or hepatotoxicity).*

Ryley NG, Forman R, Barlow D, Fleming KA, Trowell JM. Liver abnormality in ovarian hyperstimulation syndrome. Hum Reprod 1990; 5: 938-43. PubMed PMID: 1982004.

*(32 year old woman with infertility treated with human gonadotropin and embryo transfer developed nausea, abdominal distension, marked ascites and hypovolemic shock [peak bilirubin 1.5 mg/dL, AST 255 U/L, Alk P 1173 U/L], biopsy showing fatty change and focal infiltrates, resolving after "evacuation of products").*

Balasch J, Carmona F, Llach J, Arroyo V, Jové I, Vanrell JA. Acute prerenal failure and liver dysfunction in a patient with severe ovarian hyperstimulation syndrome. Hum Reprod 1990; 5: 348-51. PubMed PMID: 2112558.

*(27 year old woman with infertility developed abdominal pain, distension, ascites, nausea and dyspnea 5 days after follicular aspiration and treatment with hCG [bilirubin rising to 4.4 m/dL, ALT 49 U/L, Alk P 627 U/L], resolving within 2-3 weeks).*

Marsepoil T, Cordesse A, Varguy P, Dauptain G, Levesque P. [Hepatic involvement in the course of ovarian hyperstimulation syndrome]. Rev Fr Gynecol Obstet 1992; 87: 148-9. French. PubMed PMID: 1579800.

*(22 year old woman with infertility developed OHSS shortly after receiving clomiphene and hCG with ascites and pleural effusions [ALT rising to 40 times ULN, bilirubin and Alk P normal], biopsy showing mild portal inflammation and sinusoidal dilatation without hepatocyte necrosis, resolving within 2 months).*

Miura K, Shirasawa H, Nagata S, Komoda F, Nakajima T, Kanai K. Two cases of recurrent hepatic injury associated with early pregnancy: hCG on hepatocytes is a suspected target antigen for lymphocyte attack. Acta Pathol Jpn 1993; 43: 765-73. PubMed PMID: 8109254.

*(Two pregnant women, ages 35 and 23 years, developed liver abnormalities during the second trimester [bilirubin1.1-13.9 mg/dL, ALT 911-2060, Alk P 1-2 times ULN] that resolved after induced abortion in one and spontaneously in another, and was attributed to high circulating levels of hCG based upon positive lymphocyte transformation tests).*

Clinical assessment of recombinant human follicle-stimulating hormone in stimulating ovarian follicular development before in vitro fertilization. Recombinant Human FSH Study Group. Fertil Steril 1995; 63: 77-86. PubMed PMID: 7805928.

*(Among 123 infertile women undergoing in vitro fertilization treated with either recombinant or urinary FSH, success rates were similar and there were no differences in rates of adverse events and no cases of OHSS; no mention of ALT elevations or hepatotoxicity).*

Senturk H, Erdinç S, Tasyurekli M, Mert A, Arvas M, Sen C. Case report: liver function abnormalities in a severe case of hyperreactio luteinalis. J Gastroenterol Hepatol 1996; 11: 617-20. PubMed PMID: 8840234.

*(A 12 week pregnant 19 year old developed multicystic ovarian masses and ascites with rises in liver tests [peak bilirubin 2.0 mg/dL, ALT 214 U/L], resolving within 2-3 weeks).*

Wakim AN, Fox SD. Elevated liver function tests in a case of moderate ovarian hyperstimulation syndrome. Hum Reprod 1996; 11: 588-9. PubMed PMID: 8671272.

*(28 year old woman with infertility was treated with clomiphene and hCG for ovarian stimulation developed abdominal pain and ascites [ALT 183 U/L, bilirubin and Alk P normal], resolving within 2 weeks of onset at time of resolution of ascites).*

Nawroth F, Heinrich J, Bruns U, Wood WG. Severe ovarian hyperstimulation syndrome (OHSS) and icterus. Hum Reprod 1996; 11: 2441-2. PubMed PMID: 8981129.

*(33 year old woman with infertility treated with clomiphene and HCG developed nausea and distended abdomen with ascites and enlarged ovaries [bilirubin rising to 5.2 mg/dL, ALT 184 U/L, Alk P normal], resolving within 2-3 weeks).*

Rizk B, Aboulghar M, Smitz J, Ron-El R. The role of vascular endothelial growth factor and interleukins in the pathogenesis of severe ovarian hyperstimulation syndrome. Hum Reprod Update 1997; 3: 255-66. PubMed PMID: 9322101.

*(Review of OHSS including clinical presentation with massive cystic enlargement of ovaries and fluid shift with ascites, pleural effusions and hypovolemia caused by cytokines and growth factors [VEGF] induced by ovarian stimulation by gonadotropin therapy).*

Bergh C, Howles CM, Borg K, Hamberger L, Josefsson B, Nilsson L, Wikland M. Recombinant human follicle stimulating hormone (r-hFSH; Gonal-F) versus highly purified urinary FSH (Metrodin HP): results of a randomized comparative study in women undergoing assisted reproductive techniques. Hum Reprod 1997; 12: 2133-9. PubMed PMID: 9402268.

*(Comparison of urinary to recombinant FSH in 235 women with infertility found similar rates of successful pregnancy, but better tolerance and more reliable ovarian stimulation with rFSH, while OHSS occurred in 5.2% [rFSH] vs 1.7% [uFSH]).*

Burgués S, Calderón MD. Subcutaneous self-administration of highly purified follicle stimulating hormone and human chorionic gonadotrophin for the treatment of male hypogonadotrophic hypogonadism. Spanish Collaborative Group on Male Hypogonadotropic Hypogonadism. Hum Reprod 1997; 12: 980-6. PubMed PMID: 9194651.

*(60 men with hypogonadism were treated with FSH and hCG by self-injection 2 to 3 times weekly for 6 months; side effects included gynecomastia and headache; serum bilirubin and Alk P levels increased while mean ALT levels decreased during treatment).*

Shimono J, Tsuji H, Azuma K, Hashiguchi M, Fujishima M. A rare case of hepatic injury associated with ovarian hyperstimulation syndrome. Am J Gastroenterol 1998 Jan; 93 (1): 123-4. PubMed PMID: 9448194.

*(26 year old woman treated with menopausal gonadotropin and clomiphene to prevent spontaneous abortion developed massive ascites and multiple ovarian cysts [bilirubin 1.3 mg/dL, ALT 194 U/L] with subsequent resolution, but spontaneous abortion a few weeks later).*

Efficacy and safety of highly purified urinary follicle-stimulating hormone with human chorionic gonadotropin for treating men with isolated hypogonadotropic hypogonadism. European Metrodin HP Study Group. Fertil Steril 1998; 70: 256-62. PubMed PMID: 9696217.

*(Among 28 men with hypogonadism treated with hCG for 3-6 months followed by urinary FSH, 89% achieved spermatogenesis and side effects were uncommon and largely due to increased testosterone levels [acne, weight gain, cryptorchidism]; "clinical chemistry assays...showed no clinically relevant changes").*

Andoh K, Mizunuma H, Liu X, Kamijo T, Yamada K, Ibuki Y. A comparative study of fixed-dose, step-down, and low-dose step-up regimens of human menopausal gonadotropin for patients with polycystic ovary syndrome. Fertil Steril 1998; 70: 840-6. PubMed PMID: 9806564.

*(Among 37 women with polycystic ovary syndrome treated with various cyclic regimens of FSH injections; one patient developed severe OHSS with ascites).*

Liu PY, Turner L, Rushford D, McDonald J, Baker HW, Conway AJ, Handelsman DJ. Efficacy and safety of recombinant human follicle stimulating hormone(Gonal-F) with urinary human chorionic gonadotrophin for induction of spermatogenesis and fertility in gonadotrophin-deficient men. Hum Reprod 1999; 14: 1540-5. PubMed PMID: 10357972.

*(10 men with hypogonadism were treated with rFSH injections daily after a 6 month course of hCG: "...clinical chemistry variables were normal and entry and no significant changes were observed during treatment").*

Midgley DY, Khalaf Y, Braude PR, Nelson-Piercy C. Recurrent cholestasis following ovarian hyperstimulation syndrome: case report. Hum Reprod 1999; 14: 2249-51. PubMed PMID: 10469689.

*(34 year old woman with infertility developed OHSS 4 weeks after successful embryo transfer with ascites and enlarged ovaries [ALT 65 U/L], and then at 9 weeks developed pruritus and cholestasis of pregnancy [ALT 215 U/L, elevated bile acids] and then developed preeclampsia and cholestasis again [ALT ~350 U/L], resolving with delivery of normal twins).*

Fábregues F, Balasch J, Ginès P, Manau D, Jiménez W, Arroyo V, Creus M, et al. Ascites and liver test abnormalities during severe ovarian hyperstimulation syndrome. Am J Gastroenterol 1999; 94: 994-9. PubMed PMID: 10201472.

*(Among 50 women with OHSS admitted over a 7 year period to a single referral center, all developed ascites between 4 and 11 days after ovulation induction with gonadotropins, 15 had abnormal liver tests [bilirubin normal, ALT 51-277 U/L, Alk P 83-411 U/L], resolving within 1-3 weeks along with ascites).*

Chen CD, Wu MY, Chen HF, Chen SU, Ho HN, Yang YS. Relationships of serum pro-inflammatory cytokines and vascular endothelial growth factor with liver dysfunction in severe ovarian hyperstimulation syndrome. Hum Reprod 2000; 15: 66-71. PubMed PMID: 10611190.

*(Among 29 women with OHSS after in vitro fertilization, 15 had abnormal liver tests [bilirubin 1.2-2.6 mg/dL, ALT 35-144 U/L, Alk P 64-238 U/L]).*

Frydman R, Howles CM, Truong F. A double-blind, randomized study to compare recombinant human follicle stimulating hormone (FSH; Gonal-F) with highly purified urinary FSH (Metrodin) HP) in women undergoing assisted reproductive techniques including intracytoplasmic sperm injection. The French Multicentre Trialists. Hum Reprod 2000; 15: 520-5. PubMed PMID: 10686190.

*(Controlled trial of rFSH vs uFSH in 278 women undergoing IVF found similar rates of successful live births and similar rate of adverse events, OHSS occurring in 5% [rFSH] vs 2.2% [uFSH]).*

Burgué S; Spanish Collaborative Group on Female Hypogonadotrophic Hypogonadism. The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group I anovulation: evidence from a multicentre study in Spain. Hum Reprod 2001; 16: 2525-32. PubMed PMID: 11726569.

*(Open label study of recombinant FSH and LH in 38 anovulatory women found a high rate of follicular development and few side effects including 3 cases of OHSS: "treatment did not cause significant changes in haematological, biochemical or urinary parameters").*

Chang P, Kenley S, Burns T, Denton G, Currie K, DeVane G, O'Dea L. Recombinant human chorionic gonadotropin (rhCG) in assisted reproductive technology: results of a clinical trial comparing two doses of rhCG (Ovidrel) to urinary hCG (Profasi) for induction of final follicular maturation in in vitro fertilization-embryo transfer. Fertil Steril 2001; 76: 67-74. PubMed PMID: 11438321.

*(Among 297 infertile women undergoing assisted reproduction techniques who received either urinary hCG or one of two doses of recombinant hCG, efficacy was better with the higher dose, but side effects were more common including OHSS in 3% after uhCG and 3% and 9% after low and high dose rhCG in whom ALT levels were usually increased).*

European Recombinant LH Study Group. Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. J Clin Endocrinol Metab 2001; 86: 2607-18. PubMed PMID: 11397861.

*(Among 259 infertile women treated with rFSH for ovarian stimulation received one of 4 doses of rLH or uhCG for final follicular maturation, success rates were similar with all regimens, but OHSS was less in those who received a single dose of rLH compared to multiple doses or urinary hCG).*

International Recombinant Human Chorionic Gonadotropin Study Group. Induction of ovulation in World Health Organization group II anovulatory women undergoing follicular stimulation with recombinant human follicle-stimulating hormone: a comparison of recombinant human chorionic gonadotropin (rhCG) and urinary hCG. Fertil Steril 2001; 75: 1111-8. PubMed PMID: 11384635.

*(Controlled trial of injections of recombinant vs urinary hCG in 198 women undergoing ovarian stimulation with FSH found that local reactions were less with rhCG but all 3 cases of OHSS occurred with its use).*

Elter K, Scoccia B, Nelson LR. Hepatic dysfunction associated with moderate ovarian hyperstimulation syndrome. A case report. J Reprod Med 2001; 46: 765-8. PubMed PMID: 11547654.

*(33 year old woman with infertility developed abdominal distension, ascites and OHSS 11 days after embryo transfer with daily injections of leuprolide and several injections of FSH, hCG and progesterone [ALT 265 U/L, bilirubin and Alk P normal] resolving in 1-2 weeks).*

Davis AJ, Pandher GK, Masson GM, Sheron N. A severe case of ovarian hyperstimulation syndrome with liver dysfunction and malnutrition. Eur J Gastroenterol Hepatol 2002; 14: 779-82. PubMed PMID: 12169989.

*(28 year old woman with infertility developed abdominal pain and distension 1 day after embryo transfer [bilirubin 0.6 mg/dL, ALT 462 U/L, Alk P 706 U/L, prothrombin time 19 sec], resolving over the ensuing 3 weeks).*

Liu PY, Wishart SM, Handelsman DJ. A double-blind, placebo-controlled, randomized clinical trial of recombinant human chorionic gonadotropin on muscle strength and physical function and activity in older men with partial age-related androgen deficiency. J Clin Endocrinol Metab 2002; 87: 3125-35. PubMed PMID: 12107212.

*(Controlled trial of hCG vs placebo injected twice weekly for 3 months in 40 older men with partial androgen deficiency, found increases in serum testosterone and decreases in LH and FSH, but no improvement in muscle strength or sexual function and slight increase in body weight; no mention of ALT elevations or hepatotoxicity).*

Dickey RP, Thornton M, Nichols J, Marshall DC, Fein SH, Nardi RV; Bravelle IVF Study Group. Comparison of the efficacy and safety of a highly purified human follicle-stimulating hormone (Bravelle) and recombinant follitropin-beta for in vitro fertilization: a prospective, randomized study. Fertil Steril 2002; 77: 1202-8. PubMed PMID: 12057729.

*(Controlled trial of recombinant vs urinary FSH injections in 177 women undergoing in vitro fertilization found similar rates of efficacy and side effects with 6 cases of OHSS, one of them severe; no mention of ALT elevations or hepatotoxicity).*

Bouloux P, Warne DW, Loumaye E; FSH Study Group in Men's Infertility. Efficacy and safety of recombinant human follicle-stimulating hormone in men with isolated hypogonadotropic hypogonadism. Fertil Steril 2002; 77: 270-3. PubMed PMID: 11821082.

*(Among 19 infertile men treated with recombinant FSH injected 3 times weekly for 18 months to stimulate spermatogenesis, side effects were largely due to increase in testosterone levels; no mention of ALT elevations or hepatotoxicity).*

Delvigne A, Rozenberg S. Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). Hum Reprod Update 2003; 9: 77-96. PubMed PMID: 12638783.

*(Review of OHSS mentions that liver abnormalities occur in 26-40% of cases, typically with elevations in ALT, but normal bilirubin and Alk P values, resolving in all cases with resolution of the syndrome).*

López E, Gunby J, Daya S, Parrilla JJ, Abad L, Balasch J. Ovulation induction in women with polycystic ovary syndrome: randomized trial of clomiphene citrate versus low-dose recombinant FSH as first line therapy. Reprod Biomed Online 2004; 9 (4): 382-90. PubMed PMID: 15511336.

*(Among 76 women with infertility and polycystic ovarian syndrome treated with 3 cycles of either low dose rFSH or clomiphene to induce follicular development, 2 cases of mild OHSS occurred in the rFSH treated patients and none with clomiphene; other adverse events were not mentioned).*

Keye WR, Webster B, Dickey R, Somkuti S, Crain J, Scobey MJ. Subcutaneously administered Menopur, a new highly purified human menopausal gonadotropin, causes significantly fewer injection site reactions than Repronex in subjects undergoing in vitro fertilization. Reprod Biol Endocrinol 2005; 3: 62. PubMed PMID: 16280073.

*(Among 125 women with infertility treated with leuprolide and one of two forms of human urinary menopausal gonadotropins for up to 12 days before hCG administration, side effects were with the two products, except for fewer injection site reactions with the more highly purified preparation; no mention of ALT elevations of hepatotoxicity).*

Abdelmassih V, Oliveira FG, Goncalves SP, Varella AD, Diamond MP, Abdelmassih R. A prospective, randomized and blinded comparison between 10,000 IU urinary and 250 microg recombinant human chorionic gonadotropin for oocyte maturation in in vitro fertilization cycles. J Assist Reprod Genet 2005; 22: 149-53. PubMed PMID: 16021858.

*(Controlled trial of single injections of urinary vs recombinant hCG for oocyte maturation in 100 women with infertility found similar efficacy, but more local injection site reactions with uhCG [38%] than rhCG [13%]; no mention of ALT elevations or hepatotoxicity).*

Obrzut B, Kuczy.ski W, Grygoruk C, Putowski L, Kluz S, Skret A. Liver dysfunction in severe ovarian hyperstimulation syndrome. Gynecol Endocrinol 2005; 21: 45-9. PubMed PMID: 16048801.

*(32 year old woman with infertility developed severe OHSS with marked ascites, dyspnea and hypovolemia after therapy with clomiphene and hCG [bilirubin 5 mg/dL, ALT 3372 U/L, Alk P 310 U/L], with full recovery over the ensuing month).*

Binder H, Dittrich R, Einhaus F, Krieg J, MüA, Strauss R, Beckmann MW, Cupisti S. Update on ovarian hyperstimulation syndrome: Part 1--Incidence and pathogenesis. Int J Fertil Womens Med 2007; 52: 11-26. PubMed PMID: 17987884.

*(Review of OHSS, which arises in 0.2-1% of stimulation cycles in assisted reproduction and may be mediated by VEGF levels of which correlate with hCG levels; liver enzyme elevations, predominantly ALT and AST, arise in 25-40% of cases possibly due to the increased capillary permeability of OHSS).*

Kaufmann R, Dunn R, Vaughn T, Hughes G, O'Brien F, Hemsey G, Thomson B, O'Dea LS. Recombinant human luteinizing hormone, lutropin alfa, for the induction of follicular development and pregnancy in profoundly gonadotrophin-deficient women. Clin Endocrinol (Oxf) 2007; 67: 563-9. PubMed PMID: 17692110.

*(Injections of recombinant LH and FSH were given to 31 hypogonadal women in 54 cycles of 9 to 28 days and achieved follicular development in 87%; "There were no clinically significant abnormalities for any of the blood chemistry...parameters assessed").*

Moon SY, Choi YS, Ku SY, Kim SH, Choi YM, Kang IS, Kim CH. Comparison of the efficacy and safety of a new recombinant human follicle-stimulating hormone (DA-3801) with follitropin-alpha (Gonal-F) in women undergoing controlled ovarian hyperstimulation for assisted reproductive technology. J Obstet Gynaecol Res 2007; 33: 305-15. PubMed PMID: 17578360.

*(Controlled trial of two formulations of rFSH in 97 women undergoing ovarian stimulation found similar rates of efficacy and side effects; there were minor changes in ALT and Alk P levels, "but these changes were within reference ranges and not clinically significant").*

Shoham Z, Smith H, Yeko T, O'Brien F, Hemsey G, O'Dea L. Recombinant LH (lutropin alfa) for the treatment of hypogonadotrophic women with profound LH deficiency: a randomized, double-blind, placebo-controlled, proof-of-efficacy study. Clin Endocrinol (Oxf) 2008; 69: 471-8. PubMed PMID: 18485121.

*(Among 39 women with infertility treated with recombinant FSH and either recombinant LH or placebo in an attempt to stimulate follicular development, the addition of rLH provided a higher rate of follicular development, but no difference in rates of adverse events; one placebo recipient had a transient ALT elevation).*

Drugs for ovulation induction. Med Lett Drugs Ther 2011; 53 (1376): 86-8. PubMed PMID: 22033212.

*(Concise review of the efficacy and safety of drugs used for ovarian induction mentions that common side effects of FSH, LH and hCG include injection site reactions, headache, abdominal pain and nausea, and that FSH and LH can cause OHSS which can be severe and even fatal; no mention of ALT elevations or hepatotoxicity).*

Ashrafi M, Kiani K, Ghasemi A, Rastegar F, Nabavi M. The effect of low dose human chorionic gonadotropin on follicular response and oocyte maturation in PCOS patients undergoing IVF cycles: a randomized clinical trial of efficacy and safety. Arch Gynecol Obstet 2011; 284: 1431-8. PubMed PMID: 21210134.

*(Among 90 women with polycystic ovary syndrome undergoing assisted reproduction treated with FSH and with one of three regimens of hCG to induce ovulation, severe OHSS occurred only in those in whom FSH was continued in full dosage).*

Checa MA, Espinós JJ, Requena A. Efficacy and safety of human chorionic gonadotropin for follicular phase stimulation in assisted reproduction: a systematic review and meta-analysis. Fertil Steril 2012; 97: 1343-50. e1-3. PubMed PMID: 22464087.

*(Systematic review of the literature on use of hCG for follicular phase stimulation identified 11 relevant publications; discussion of adverse events was restricted to miscarriage and OHSS, neither of which was more frequent with hCG than with comparator treatments such as FSH and LH).*

Alviggi C, Cognigni GE, Morgante G, Cometti B, Ranieri A, Strina I, Filicori M, et al. A prospective, randomised, investigator-blind, controlled, clinical study on the clinical efficacy and tolerability of two highly purified hMG preparations administered subcutaneously in women undergoing IVF. Gynecol Endocrinol 2013; 29: 695-9. PubMed PMID: 23638621.

*(Among 157 women receiving one of two menopausal gonadotropin preparations as a part of assisted reproductive techniques, success rates and adverse event rates were similar, two women developed mild OHSS, no mention of ALT elevations or hepatotoxicity).*

Figueiredo JB, Nastri CO, Vieira AD, Martins WP. Clomiphene combined with gonadotropins and GnRH antagonist versus conventional controlled ovarian hyperstimulation without clomiphene in women undergoing assisted reproductive techniques: systematic review and meta-analysis. Arch Gynecol Obstet 2013; 287: 779-90. PubMed PMID: 23250342.

*(Review of 7 studies comparing the safety of regimens to induce ovulation with or without clomiphene mentions that OHSS is less common in regimens that include clomiphene [0.5% vs 4%]).*

Bellavia M, de Geyter C, Streuli I, Ibecheole V, Birkhäer MH, Cometti BP, de Ziegler D. Randomized controlled trial comparing highly purified(HP-hCG) and recombinant hCG (r-hCG) for triggering ovulation in ART. Gynecol Endocrinol 2013; 29: 93-7. PubMed PMID: 23116325.

*(Among 147 women receiving either recombinant or highly purified urinary hCG preparations while undergoing assisted reproductive techniques, adverse event rates were similar and 5 women developed moderate-to-severe OHSS; no mention of ALT elevations or hepatotoxicity).*

Chalasani 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. PubMed PMID: 25754159.

*(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to gonadotropins or arose as a complication of assisted reproductive techniques).*

Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril 2016; 106: 1634-47. PubMed PMID: 27678032.

*(Guidelines on management and prevention of OHSS, an uncommon but serious complication of assisted reproductive techniques occuring in 1-5% of cycles, severe instances accompanied by abdominal pain, ascites and liver enzyme elevations; rates are higher with GnRH agonists than antagonists).*

Humaidan P, Chin W, Rogoff D, D'Hooghe T, Longobardi S, Hubbard J, Schertz J; ESPART Study Investigators. Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. Hum Reprod 2017; 32: 544-55. PubMed PMID: 28137754.

*(Among 939 women who had a poor response to ovarian stimulation during assisted reproductive technology [ART] and who underwent repeat ART with either recombinant hFSH alone or its combination with recombinant hLH, rates of oocyte retrieval were similar as were adverse event rates; only one patient developed OHSS which was mild and self-limited).*