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Delayed Fulminant Hepatic Failure from Dydrogesterone-Related *In Vitro* Fertilization Therapy Requiring Liver Transplantation During Pregnancy

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Data Collection B
Statistical Analysis C
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Manuscript Preparation E
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ABCDEF 1,2
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ABCDE 4
ABCDEF 1,2,3
Jacques A.J. Malherbe
George Garas
Tze S. Khor
Gerry C. MacQuillan

1 Department of Hepatology, Sir Charles Gairdner Hospital, Nedlands, WA, Australia
2 Medical School, University of Western Australia, Crawley, WA, Australia
2 Western Australia Liver Transplantation Service, Sir Charles Gairdner Hospital, Nedlands, WA, Australia
4 Department of Anatomical Pathology, PathWest Laboratory Medicine, Nedlands, WA, Australia

Corresponding Author: Gerry C. MacQuillan, e-mail: gerry.macquillan@health.wa.gov.au
Conflict of interest: None declared

Patient: Female, 35-year-old
Final Diagnosis: Fulminant liver failure
Symptoms: Coagulopathy • hepatic encephalopathy • jaundice
Medication: —
Clinical Procedure: Liver transplantation
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course

Background: Drug-induced liver failure is a rare complication of pregnancy and occasionally requires liver transplantation. However, fulminant liver failure arising from *in vitro* fertilization (IVF) therapy involving progestogens (e.g. dydrogesterone) is extremely rare and has not been reported in pregnancy. Furthermore, dydrogesterone-mediated hepatic dysfunction has not previously necessitated liver transplantation and is usually conservatively managed. We report the first Australian case of a pregnant woman with delayed fulminant liver failure and *in utero* fetal death requiring a liver transplant from dydrogesterone use.

Case Report: A 35-year-old multiparous (G₅P₂) woman presented with painless jaundice and transaminitis (alanine aminotransferase and aspartate aminotransferase of 2800 U/L and 2990 U/L respectively). She was pregnant at 14 weeks' gestation after successful IVF in Thailand four months before involving dydrogesterone therapy. She was diagnosed with delayed, subfulminant liver failure arising from previous dydrogesterone use. Initially, she was not encephalopathic and conservative management strategies were instituted. Her hepatic dysfunction progressed and she deteriorated clinically with encephalopathy, necessitating an emergent liver transplantation. Fetal death was confirmed *in utero* four days before transplantation. A combined orthotopic liver transplant and hysterectomy with fetal evacuation were performed without complication.

Conclusions: Fulminant liver failure in pregnancy due to idiosyncratic drug reactions are rare. Dydrogesterone may cause significant, albeit delayed, liver dysfunction in pregnancy necessitating the need for liver transplantation. Early recognition of progressive liver failure despite best supportive care efforts should prompt early considerations for liver transplantation. Delays in liver transplantation with prolonged hyperbilirubinemia and coagulopathy may exacerbate fetal death *in utero*.


MeSH Keywords: Dydrogesterone • Liver Failure, Acute • Liver Transplantation • Pregnancy

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Background

Fulminant liver failure represents a rare complication of pregnancy and is more common during the third trimester [1]. Half of these cases are attributable to hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, and acute fatty liver of pregnancy (AFLP) [1–3]. The remainder are caused by severe viral hepatitis, particularly hepatitis E in the developing world, as well as intrahepatic cholestasis of pregnancy (ICP), drug-induced liver injury, and Budd Chiari syndrome secondary to hepatic vein thrombosis [1–9]. A significant proportion of cases are often cryptogenic in their etiology [10–16]. Acute liver failure occurring during the first and second trimesters of pregnancy are associated with poor fetal outcomes, including developmental delays, neurological abnormalities, spontaneous abortions, and neonatal death [6–16]. However, only ~16% of pregnant women with fulminant liver failure will require liver transplantation [2].

Drug-induced liver injury in pregnancy seldom causes fulminant hepatic failure requiring liver transplantation [5,7–9]. The most frequently implicated agents include acetaminophen, isoniazid, valproate, phenytoin, and propylthiouracil [5]. The latter has caused fulminant liver failure in two pregnant patients requiring emergency liver transplantation [7,8]. Of these, only one case resulted in fetal preservation and delivery of an infant at 37 weeks' gestation with significant neurological morbidity and developmental delay [8]. Fulminant liver failure arising from *in vitro* fertilization (IVF) therapies, particularly progestogens (eg dydrogesterone), are extremely rare. Multiple trials and reviews have evaluated the safety profile of dydrogesterone use in IVF and have reported minimal adverse side effects (ie nausea, vomiting, dizziness, constipation) [17]. No large cohort study or trial to date has shown any hepatic dysfunction arising from dydrogesterone [17]. Only two case reports have associated the use of dydrogesterone with the development of jaundice, acute hepatitis, and in one of these patients, comorbid autoimmune hemolytic anemia [18,19]. However, neither patient achieved pregnancy nor required a liver transplant.

We report the first Australian case of a 35-year-old multiparous, pregnant woman requiring an emergency liver transplant secondary to dydrogesterone-induced fulminant hepatic failure with associated fetal death. We demonstrate that dydrogesterone-induced liver failure in pregnancy may be delayed. This case highlights the need for early liver transplantation in progressive drug-induced liver failure despite the best supportive care efforts. Furthermore, delays in transplantation that prolong maternal hyperbilirubinemia and coagulopathy may exacerbate fetal death.

Case Report

A 35-year-old multiparous (G₅P₂) Australian woman of Indian descent at 14 weeks' gestation, previously fit and well, was admitted to our hepatology service for investigation and management of painless jaundice and elevated transaminases. The patient had reported the onset of scleral jaundice three days before her hospital admission with associated pruritus affecting the palms of her hands and soles of her feet. She denied any abdominal, stool, or urinary symptoms. Her past medical history included previous gestational diabetes, an elective termination of pregnancy four years prior, and a left salpingectomy one year ago after a previous ectopic pregnancy. She had undergone two previous spontaneous vaginal deliveries at term without complication. Her previous term pregnancies were unremarkable, with no prior history of liver dysfunction, eclampsia, HELLP, AFLP, or ICP. She had no history of any underlying liver or gallbladder disease. She did not smoke or drink alcohol. She did not have any tattoos and had no previous blood transfusions.

She had traveled to Thailand approximately four months before her hospital admission for IVF therapy. She had received a regular IVF regimen comprising three months' duration of oral dydrogesterone (10 mg), oral estradiol (1 mg), and per vaginal progesterone. Embryo transfer and implantation was successful, and she returned to Australia for ongoing antenatal care. She reported only taking routine pregnancy supplements including Ferrograd-C, vitamin B complex, and cholecalciferol while pregnant. She did not use any herbal supplements, analgesic agents, antibiotics, or over-the-counter medications. On examination, she was hypotensive at 90/60 mmHg, but her other vitals were within normal limits. She was clinically jaundiced with evidence of marked scleral icterus. Peripheral stigmata of chronic liver disease were absent. She had no features of hepatic encephalopathy. Abdominal examination revealed a smooth liver edge that was nontender. Her abdomen was soft with no evidence of ascites.

Peripheral blood investigations on admission (day 0, Figure 1) noted abnormally elevated transaminases (ie alanine aminotransferase [ALT] 2800 U/L and aspartate aminotransferase [AST] 2990 U/L), and albumin of 36 g/L. Total and conjugated bilirubin levels were elevated at 215 µmol/L and 183 µmol/L respectively. Her international normalized ratio (INR) was mildly elevated at 1.3 with a normal platelet count of 310×10⁹/L. Her liver enzyme profile was within normal limits before this pregnancy. Elevations of her total white cell count (11.98×10⁹/L), neutrophils (8.39×10⁹/L), ferritin (1260 µg/L), and lactate dehydrogenase (672 U/L) were noted. Her hemoglobin and eosinophil counts were normal at 144 g/L and 0.24×10⁹/L respectively. Blood film analysis showed no features of hemolysis, including echinocytes and erythrocyte fragments. A hemolysis

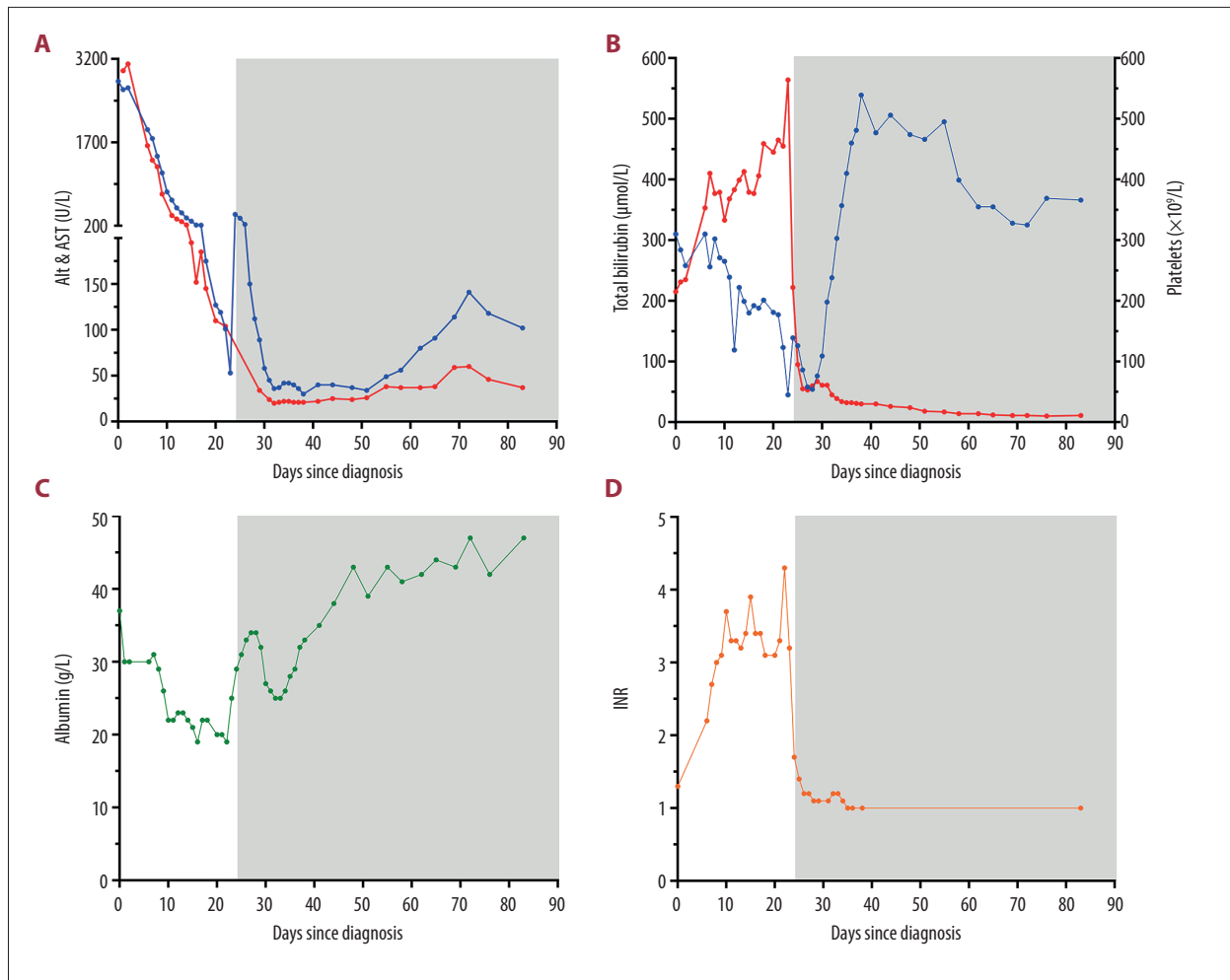


Figure 1. Longitudinal biochemical data illustrating the patient's progressive hepatic failure since her hospital admission (day 0). Transplantation occurred at day 24 with subsequent post-transplant biochemical data illustrated thereafter by gray shading. (A) Alanine aminotransferase (ALT, blue) and aspartate aminotransferase (AST, red) parameters showing initial significant transaminitis with progressive normalization post-liver transplantation. Hepatic failure was further illustrated by progressive (B) hyperbilirubinemia (red), thrombocytopenia (blue), (C) hypoalbuminemia, and (D) coagulopathy (international normalized ratio [INR]). Post-transplantation, all parameters normalized.

screen was unremarkable, including normal haptoglobin and reticulocyte counts with negative Coombs' test. Uric acid levels were normal (0.18 mmol/L). Urinalysis and culture were unremarkable, with normal urine albumin (<2.0 mg/L) and urine albumin/creatinine ratio (<0.1 mg/mmol). A urine drug screen was not performed. Additional serology, stool, and viral polymerase chain reaction testing for hepatitis viruses A through to E, Epstein-Barr virus, cytomegalovirus (CMV), human immunodeficiency virus, herpes simplex virus, adenovirus, human herpesvirus-6, *Leptospira*, and *Listeria* species were negative. Sputum and serological testing for tuberculosis were negative. An autoimmune screen including antinuclear antibody, anti-neutrophilic cytoplasmic antibody, anti-smooth muscle antibodies, anti-liver-kidney microsome antibody, mitochondrial antibodies, anti-soluble liver antigen antibodies, anti-liver

cytosol-1 antibodies, and immunoglobulin levels were unremarkable. Alpha-1 anti-trypsin levels were normal. Vitamin D levels were replete at 72 nmol/L. Her estradiol level was 33 000 pmol/L. Follicle-stimulating hormone and luteinizing hormone levels were <0.1 and 0.2 U/L respectively. All other routine biochemistry was unremarkable. Routine Doppler ultrasonography of the liver and abdomen performed on admission revealed normal appearances with no focal hepatic lesions, thromboses, or biliary dilatation. A viable fetus was noted at this time. Features of HELLP, AFLP, ICP, and infective etiologies for her liver failure were excluded on the basis of the above investigations.

Supportive care was initiated during her admission including an *N*-acetyl infusion, albumin, and vitamin K supplementation.

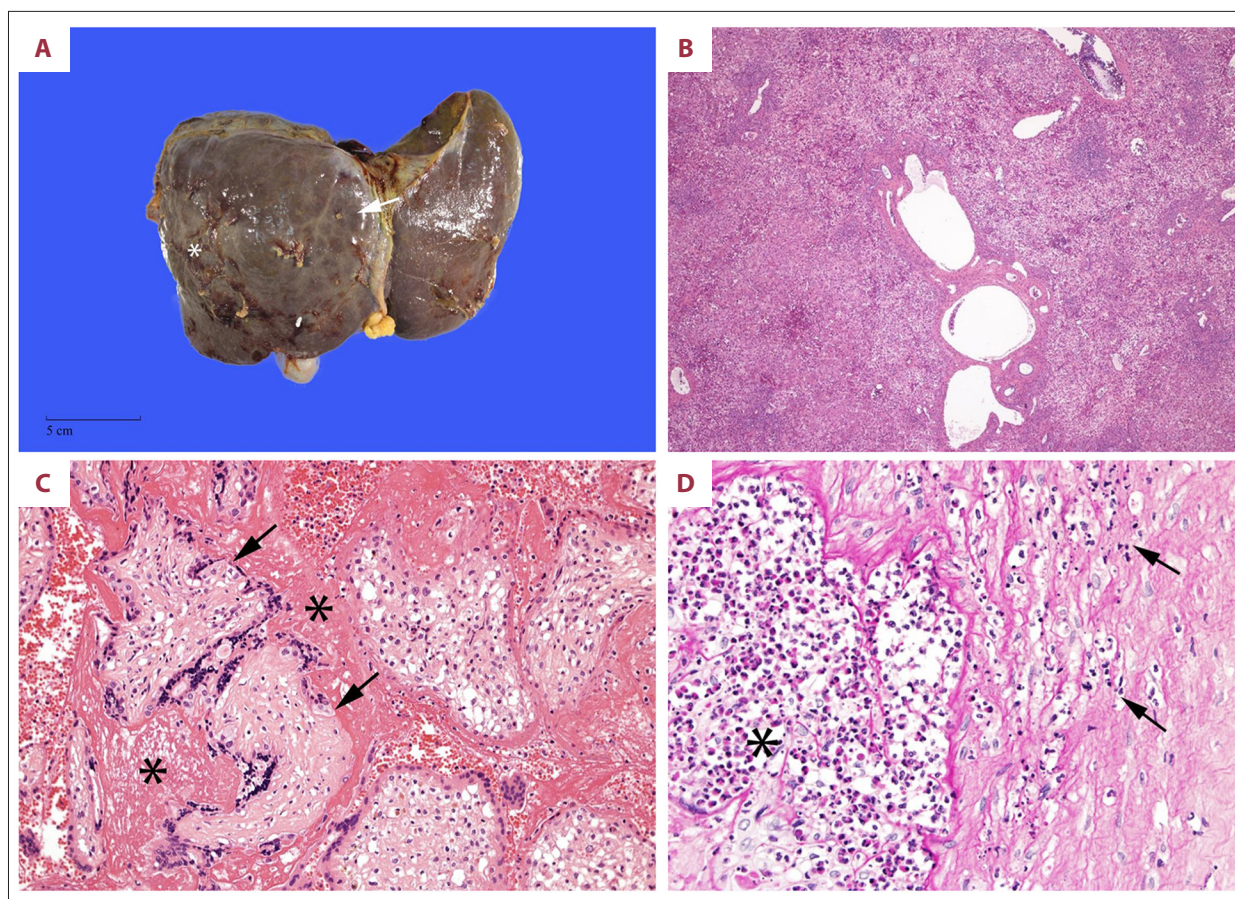


Figure 2. Representative macroscopic and microscopic images of the patient's liver and placenta. (A) Gross morphology of the liver with submassive hepatic necrosis demonstrating capsular wrinkling and flattening (*) with developing regenerative nodularity (arrow) in portions of the liver. (B) Histologic examination of the liver demonstrating submassive hepatic necrosis characterized by complete loss of hepatocytes and inflammation (right and upper portion of image), with early regenerative nodularity (lower left portion of image). (Original magnification $\times 40$.) (C) Histologic examination of the placenta demonstrating evidence of chorioamnionitis characterized by subchorionic fibrin (*) with admixed neutrophils and neutrophilic infiltration of the chorionic plate (arrows). (Original magnification $\times 400$.) (D) Histologic examination of the placenta demonstrating extensive accumulation of intervillous blood with perivillous fibrin deposition (*) and early ischemic change of villi (arrows). (Original magnification $\times 200$.)

Her ALT and AST levels declined (Figure 1A) over the next week. However, ongoing biochemical deterioration was observed, including profound exacerbations of her hyperbilirubinemia, thrombocytopenia, hypoalbuminemia, and associated coagulopathy (Figure 1B–1D). At this time, she remained clinically asymptomatic and was not encephalopathic, excluding her persistent jaundice. Serum ceruloplasmin levels were within normal limits, but a 24-hour urine copper collection revealed a mildly elevated copper level ($3.66 \mu\text{mol/day}$, reference range: $<0.5 \mu\text{mol/day}$). An atypical form of Wilson's disease unmasked by the current pregnancy was considered. She proceeded to have an ophthalmic review and Kayser-Fleischer rings were excluded. Concurrently, a transjugular biopsy of our patient's liver was collected and showed features of submassive hepatic necrosis involving $\sim 40\%$ of the parenchyma without fibrosis. Focal steatosis with variable ballooning and cholestasis were

noted. Predominant Kupffer cells and lymphocyte infiltrates were seen admixed among neutrophils and eosinophils. The liver biopsy dry copper weight was normal (0.5 mmol/kg , reference range: $<0.6 \text{ mmol/kg}$) and Wilson's disease was excluded. Possible differential diagnoses considered at this time included a drug-induced liver injury (ie dydrogesterone), toxic hepatic injury, or an undiagnosed fulminant viral hepatitis.

Despite our best supportive care efforts, our patient continued to deteriorate biochemically (Figure 1). She was activated for liver transplantation on day 10 of her admission and an urgent multidisciplinary liver transplantation workup as per our local hospital protocols and national policies was undertaken. Obstetric experts were consulted. A termination of the previable fetus before liver transplantation was not recommended. Although the fetus was at high risk of not surviving the current

state of maternal liver failure, liver transplantation during pregnancy was considered a viable option that may sustain fetal survival. At day 21–22 after her initial admission, the patient clinically decompensated and became acutely encephalopathic. Her Glasgow coma scale decreased (E3V4M6) and she developed a new sinus tachycardia (130 beats per min) with oliguria. Her biochemistry at this time showed an ALT 119 U/L, AST 110 U/L, total bilirubin 465 $\mu\text{mol/L}$, albumin 19 g/L, platelet count $123 \times 10^9/\text{L}$, creatinine 142 $\mu\text{mol/L}$, and INR 4.3. She was admitted to the intensive care unit for ongoing management. A repeat Doppler ultrasound was performed and showed new ascites with increased echogenicity of the liver. An obstetric ultrasound was also performed, which confirmed fetal death *in utero* at 17+5 weeks' gestation. Obstetric opinion recommended that the deceased fetus not be evacuated before the liver transplantation unless she developed severe per vaginal bleeding in her current coagulopathic state. Central venous access was obtained, and she was fluid resuscitated with crystalloid and albumin replacement. Intravenous terlipressin and, later, continuous venous-venous hemodiafiltration were instituted to support her hepatorenal syndrome. She was transfused with fresh frozen plasma, cryoprecipitate, vitamin K, and tranexamic acid to correct her underlying coagulopathy. Chest radiography noted progressive pulmonary edema and with the progressive deterioration in her conscious state, she was subsequently intubated and ventilated.

Her model for end-stage liver disease (MELD) score at this time was 40. A liver from a dead donor was obtained from a neighboring state within 48 hours. On day 24 after her initial hospital admission, the patient underwent a combined orthotopic liver transplantation with hysterotomy and evacuation of the deceased fetus without significant intraoperative complication. Histopathological analysis of the explanted liver (Figure 2) showed submassive hepatocellular necrosis with admixture of confluent necrosis (involving >50% of hepatic parenchyma) and regenerative nodules. There was no evidence of any underlying dysplastic, neoplastic, or infiltrative disorders (eg iron, copper). Features were in keeping with drug-induced fulminant hepatic failure, likely secondary to previous dydrogesterone use. Placental histology showed features of acute chorioamnionitis with early fibrin deposition and ischemic necrosis (Figure 2).

Our patient's postoperative course was essentially unremarkable. She continued to improve clinically and biochemically, with resolution of her transaminitis, coagulopathy, and jaundice (Figure 1). Her post-transplant immunosuppression regimen consisted of tacrolimus 4 mg twice a day, azathioprine 75 mg daily, and weaning prednisolone. Valganciclovir 900 mg daily and Bactrim 800/160 mg thrice weekly were provided routinely for CMV and *Pneumocystis jirovecii* pneumonia prophylaxis respectively. Psychological support was offered through our local Perinatal Loss Support Service. Regular outpatient

follow-up and biochemical monitoring were performed. Mild elevations in the patient's transaminases were noted at ~68–70 days after the patient's initial admission to hospital. A repeat abdominal Doppler ultrasound was performed and no underlying liver pathology was identified. She continues to remain well and is planning a future pregnancy.

Discussion

Drug-induced liver failure in pregnancy is an uncommon event and represents a diagnosis of exclusion [5]. Offending agents typically include acetaminophen and occasionally propylthiouracil, and if fulminant or progressive, may necessitate a liver transplant [5,7–9]. Hepatic injury related to IVF drugs is rare. ICP secondary to IVF occurs in 0.01–2.7% of pregnancies [4,20,21]. Dydrogesterone-related hepatic failure has not been previously reported in pregnancy [17]. To the best of our knowledge, we have reported the first Australian case of a multiparous pregnant woman with dydrogesterone-induced fulminant hepatic failure requiring a liver transplant complicated by fetal death during the second trimester.

Dydrogesterone is an old progestogen that has been available since the 1970s [17]. It is still commonly used in several developing countries for routine IVF therapy with significant efficacy. In comparison with other IVF options, dydrogesterone has minimal maternal adverse side effects and holds a reputable safety profile among multiple clinical trials and reviews [17]. However, recent reports have associated its use with profound neurological, genital, and cardiological abnormalities in the developing fetus [22]. To date, liver dysfunction associated with dydrogesterone use has only been reported in two patients from Turkey and Malaysia with mild, self-resolving hepatitis [18,19]. In both cases, the onset of jaundice and hepatitis occurred within two weeks of commencing dydrogesterone. The Turkish patient presented with recurrent bouts of hepatitis after dydrogesterone use over a four-year period with comorbid autoimmune hemolytic anemia, suggesting an underlying autoimmune hepatitis etiology [19]. In contrast, there was a significant delay of four months before our patient developed rapidly progressive hepatic failure requiring liver transplantation. The mechanisms underpinning dydrogesterone-mediated liver injury are not understood. Mustafa and coworkers (2014) have proposed that it potentially mimics ICP by means of upregulating estradiol [18]. Peak estradiol levels in the third trimester, when ICP is particularly prevalent, may promote cholestasis by unknown signaling cascades [4,18]. Others have suggested a similar role for progesterone and its metabolites, which are similarly found to be upregulated in ICP [4]. It is plausible that concurrent estrogen administration with dydrogesterone during IVF therapy may have potentiated our patient's hepatic failure through an ICP-mediated process. However, Germain et al. [23] have

shown that no serological differences exist in estrogen levels between women with normal pregnancies and ICP, limiting the utility of its routine measurement in IVF pregnancies. Others have also shown that elevated bile acids in IVF pregnancies are more frequently associated with ICP, but its clinical sensitivity in predicting ICP remains uncertain [24]. Altintas et al. (2004) have proposed that dydrogesterone may facilitate hepatic injury through an idiosyncratic reaction that involves a complex, albeit unknown, interplay between genetic and autoimmune factors that influence the metabolism of itself and its downstream metabolites [19]. Moreover, its hepatotoxic effects are unpredictable and can last up to several months before becoming clinically evident [19]. Overall, the idiosyncrasy of dydrogesterone in mediating hepatocellular necrosis and progressive liver failure remains to be elucidated.

Greenberg and colleagues (2009) previously established an algorithm for managing acute liver failure in pregnancy [13]. Under these circumstances, maternal survival outweighs fetal welfare, irrespective of the stage of pregnancy. Should the fetus be pre-viable (≤ 20 – 25 weeks' gestation), careful consideration toward a termination of pregnancy versus ongoing maternal and fetal support should be given, particularly as the latter carries significantly higher morbidity and mortality. Reviews of previous case reports and cohort studies have shown that fetal death during pregnancy both pre- and post-liver transplantation is high (up to 23.8%), particularly during the second trimester [1–3,5–7,9–11,15]. Of those that survive, developmental delays arising from neurological sequelae are occasionally reported [8]. Development and maturation of the central nervous system occurs during week three of embryogenesis until the 16–17th week of gestation [25]. The fetus is particularly sensitive to maternal coagulopathy and hyperbilirubinemia, with the former contributing to placental ischemia and fetal death [26,27]. Persistent placental ischemia and dysfunction may inadvertently facilitate the placental transfer of excess bilirubin more readily to the fetus, exacerbating cerebral neurotoxicity through several molecular mechanisms [28]. It is likely that the onset of severe hyperbilirubinemia and coagulopathy in our patient caused significant impaired neurological development in the fetus at a time when its central nervous

system was developmentally sensitive and did not support life. To our knowledge, no study to date has isolated the overall thresholds for hyperbilirubinemia and coagulopathy parameters that may predict fetal death. Further, the temporal relationship involving a pre-viable fetus' ability to withstand such serological abnormalities and its gestation period in relation to its survival have not been established. Nevertheless, recognition of progressive hepatocellular necrosis through persistent hyperbilirubinemia, coagulopathy, and pseudo-“improvements” in transaminases should prompt early progression toward liver transplantation during pregnancy, which may enable fetal survival and avoid significant neonatal morbidity.

Conclusions

Dydrogesterone-mediated hepatic injury and progression to fulminant hepatic failure is an extremely rare event during pregnancy. It represents an idiosyncratic reaction that may mimic ICP through excess estrogen- and progesterone-mediated effects [4,18,19]. Progressive liver failure despite conservative management strategies should prompt an early consideration for liver transplantation. Maternal well-being in these circumstances outweighs fetal survival, but the latter can be augmented by early liver transplantation and effective resolution of maternal coagulopathy and hyperbilirubinemia.

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Conflicts of interest

None.

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