



Emerging Medical Treatments of Intrahepatic Cholestasis of Pregnancy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Although intrahepatic cholestasis of pregnancy is not a serious one, it can be very distrustful to the affected women. It can also lead to significant complications and adverse events over the fetus as what has been previously reported that it is linked with stillbirth, fetal distress, and premature labor, especially in severely affected cases. Many treatment modalities have been proposed to relieve pruritis and enhance the levels of bile acids within the serum of the affected women. The administration of ursodeoxycholic acid has been studied by various studies in the literature, and evidence is conflicting about its potential efficacy and safety. However, recent evidence for a meta-analysis indicates that the modality can reduce pruritis. Nevertheless, the effect is minimal and not significant when compared to the placebo group. No significant differences were also noticed between the placebo and treatment groups. We also found that other treatment modalities than

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ursodeoxycholic acid can also be administered. Nonetheless, these were not adequately discussed in the literature, and therefore, should be cautiously administered within the clinical settings. Finally, further trials are needed to validate of the current evidence and enhance the quality of reporting and planning proper management guidelines.

Keywords: Cholestasis; pregnancy; pruritis; treatment; ursodeoxycholic acid.

1. INTRODUCTION

Intrahepatic cholestasis of pregnancy, or obstetric cholestasis, is a hepatic condition that usually affects pregnant women in the third trimester. Although the condition is not a serious one, it can be very distrustful to the affected women. It can also lead to significant complications and adverse events over the fetus as what has been previously reported that it is linked with stillbirth, fetal distress, and premature labor, especially in severely affected cases [1-3]. The exact physiology of developing the condition is not entirely understood, however, it has been suggested that endocrinal, genetic, and environmental factors usually have essential roles [4-6].

The incidence of the condition is relatively variable among the different ethnic groups. Estimates show that the prevalence of the condition can be less than 1% of pregnancies in North America, Western and Central Europe, and Australia, up to 1-2% in the Baltic states and Scandanavia, and 5-15% in Bolivia, Chile, and Araucanian Indians [7]. After 30 weeks of gestation, affected women usually present with pruritis with an absence of rash, and this clinical presentation can furtherly worsen when pregnancy advances [8,9]. Jaundice, steatorrhea, dark urine, and postpartum hemorrhage might also occur. However, these are rare conditions. Besides, the condition might also have a significant impact on the pregnancy, and therefore, conducting early, and adequate investigations are critical to enhancing the outcomes [10-12].

Many treatment modalities have been proposed to relieve pruritis and enhance the levels of bile acids within the serum of the affected women. In the present literature review, we will discuss the emerging medical treatments of intrahepatic cholestasis of pregnancy.

1.1 Overview

Many treatment approaches have been indicated in the management of intrahepatic cholestasis of

pregnancy. Medical treatments are essential and have been investigated by a variety of investigations. Several treatment approaches have been validated. However, the most important one that has been extensively studied among different studies is ursodeoxycholic acid. The main aim of the administration of medical treatment modalities for the affected pregnant women has been demonstrated to relieve pruritis. Moreover, it has been reported that the administration of 10-20 mg/kg/day of ursodeoxycholic acid is recommended as the firstline of treatment of this condition as it has been previously indicated that it can significantly enhance liver functions and lead to favorable outcomes, according to the European Association for the Study of Liver [13]. It should be noted that this treatment modality is remarkably different from other treatment approaches that are indicated for other cholestatic disorders. In such cases, anion exchange resins are usually initially administered and might include colestipol, cholestyramine, or colesevelam, in addition to the administration of other treatment modalities as serotonin receptor agonistic, rifampin, and opioids. Most of these treatment modalities are usually empirically administered. The role of administration of them is binding with bile acids within the intestinal lumen (as reported with guar gum, cholestyramine, activated charcoal, ondansetron as serotonin-receptor agonists, and naloxone as opioids), enhancing methylation and biliary excretion of hormonal metabolites (as reported with S-adenosylmethionine), detoxification of the epimedium and the hydrophobic bile acids that can lead to fluidity recover within the hepatocytic membrane (as reported with rifampin, phenobarbital, CYP450, and enzymatic inducers), and suppressing estrogen production from the fetus (as reported with dexamethasone administration) [7,13]. In 2013, a Cochrane review concluded that the evidence regarding the administration of guar gum, S-adenosylmethionine, dexamethasone, activated charcoal, Salvia, cholestyramine, Yiganling, or Yiganling and Danxioling, and Yin Cheng Hao decoction is limited, and no effectiveness was

adequately validated for the management of intrahepatic cholestasis of pregnancy [14]. This has been furtherly indicated in the more updated systematic review in 2020 [15]. Therefore, unless validation of these modalities has been indicated by further investigations, these should not be administered to manage cases with intrahepatic cholestasis of pregnancy. It should also be noted that up to the moment, no medical treatment has been approved for the management of intrahepatic cholestasis of pregnancy. However, ursodeoxycholic acid has been variously studied among the different studies in the literature more than other treatment modalities.

1.2 Ursodeoxycholic Acid

This compound is a bile acid derivative that is naturally occurring and has been reported to have an anticholestatic action within the human body effectively. It has been reported that modality is used as an off-label choice in the management of intrahepatic cholestasis of pregnancy. Many mechanisms have been reported with the drug to reduce the state of cholestasis [13,16]. Among these, it has been reported that it can significantly protect the hepatocytes and cholangiocytes of the underlying epithelium of the gall bladder from the potential cytotoxic effects of the excreted bile acids [17,18]. Besides, it can also significantly increase the excretion of bile acids and prevent stagnation by induction of bile acid transporters and increasing the synthesis and release of hepatic metabolic enzymes [19]. Many previous randomized controlled trials have evaluated the efficacy and safety of the modality in the management of pruritis secondary to intrahepatic cholestasis of pregnancy by comparing it to a placebo effect or other treatment modalities. The initial reports were found back in 1992 when Palma et al. [20] reported that the administration of ursodeoxycholic acid in a patient suffering from intrahepatic cholestasis of pregnancy was significantly associated with a reduction in the serum levels of bile acids, improved pruritis, and enhanced ALT activities with no apparent complications of side effects for both the mother and her fetus. Following this case report, many other investigations have been published with different study designs, including case reports, case series studies, and randomized controlled trials [21-25]. A previous meta-analysis has compared the findings of nine randomized controlled trials that studied the effectiveness of ursodeoxycholic acid against placebo groups,

other treatment modalities, or no treatment at all. The usually administered dose among the different studies was 450-1000 mg/day. Among the nine studies, it has been reported that a total of 454 patients were included in the final analysis. Among these patients, 207 patients were randomized to receive ursodeoxycholic acid, another 42 received cholestyramine, 70 received placebo only, 65 also received S-adenosylmethionine only, 36 received dexamethasone for one week only is followed by other two weeks of placebo administration, and only 34 of the total population were randomized to receive no treatment modalities. Resolved or reduced pruritis was significantly associated with the administration of ursodeoxycholic acid when compared to the impact of other treatment plans, in addition to reducing or normalizing the ALT levels, and decreasing the total serum levels of bile acids. Besides, less frequent adverse events were associated with the administration of ursodeoxycholic acid as compared to other treatment modalities [26]. Some of the investigated adverse events included fetal distress, spontaneous premature births, respiratory distress syndrome, and the frequency and risk of administration to the intensive care units. However, it should be noted that the reported findings were not significantly associated with the administration of ursodeoxycholic acid when compared to the placebo effect. Intrauterine fetal death was reported among two cases of the placebo group. However, no analysis was done to find a potential association between the treatment plan and these events because of the insufficient number of them [26].

A more recent trial, namely the PITCH, was not included in this analysis. This trial has included a large number of women (n= 111) that has been diagnosed with intrahepatic cholestasis of pregnancy and were randomized to receive ursodeoxycholic acid (1000-2000 mg/day) or a placebo. Although the authors reported that reduced pruritis was associated with the administration of ursodeoxycholic acid, the correlation was not adequately significant, and therefore, it was not sufficient to be recommended in this situation [27]. Moreover, it has been demonstrated that a significant reduction in the levels of serum γ -glutamyl transferase, alanine transaminase, and bilirubin, although no significant reductions were noticed in the levels of bile acids. It has furtherly been demonstrated that no differences in birth weight,

mode of delivery, blood loss, and other neonatal morbidities were associated [27]. Consequently, another meta-analysis was published and indicated that although ursodeoxycholic acid reduced pruritis, the effect was minimal on the included patients was intrahepatic cholestasis of pregnancy [14]. It should also be noted that a few adverse events, including fetal asphyxia and respiratory distress, were noticed among the treatment group. Nevertheless, the frequency was not significantly higher than the placebo one [21]. Another trial also investigated the effectiveness of 450 mg/day of ursodeoxycholic acid and indicated that the modality was associated with enhanced levels of hepatic transaminases and pruritis scores [28]. In the updated Cochrane meta-analysis, where 24 trials that recruited a total of 2007 women were included in the analysis, the authors indicated that the effect of ursodeoxycholic acid was slightly notable on reducing pruritis of intrahepatic cholestasis of pregnancy when compared to placebo. Besides, the analysis also indicated that the associated adverse events of both groups did not significantly differ due to the small sizes of the included investigations. Therefore, the authors recommended that further trials should be conducted with adequate populations and proper randomization to adequately validate the outcomes and help healthcare officials to draw better recommendations and guidelines [15]. It has been previously suggested that having a genetic condition (including a variant of ABCB4), the administration of ursodeoxycholic acid for a lifelong period should be adequately discussed [29].

1.3 Other Treatment Modalities

According to the EASL guidelines, it has been demonstrated that rifampicin should be administered as the second-line treatment of cholestasis-induced pruritis [13]. It has been reported that rifampicin can also relieve pruritis that occurs secondary to intrahepatic cholestasis of pregnancy. A previous investigation reported that combining the administration of rifampicin with the ursodeoxycholic acid was significantly associated with improved outcomes in patients that were not responsive to ursodeoxycholic acid alone treatment as assessed by the expected improvements in the serum levels of bile acids or reduced pruritis [16]. Another investigation also described and explained that the combination of rifampicin and ursodeoxycholic acid has been

associated with liver elimination and detoxification functions [30]. Oral contraceptives were also suggested to be administered by patients with a history of developing intrahepatic cholestasis of pregnancy because of the possible association between estrogen and the development of the condition. However, it is also recommended to advise these patients about the potential risk of developing pruritis secondary to the administration of these pills. Expert opinion should be provided by the physician by elevation of the liver enzymes and functions, and the administration of the combination of contraceptives should be synchronized with the status of liver enzymes following delivery [31]. Another treatment modality that has been previously reported to be beneficial in cases of intrahepatic cholestasis of pregnancy-induced pruritis is the administration of antihistaminics which have been reported to ameliorate the condition, especially in cases with nocturnal itching. In cases of malabsorption, studies also suggested the administration of vitamin K in patients suffering from long-standing cholestasis [7,32]. However, such evidence was not supported by previous randomized controlled trials, and therefore, should not be considered for practice until further validation has been provided. Oral supplementations were also reported to have a counterintuitive effect on cholestasis. Therefore, it has no longer been suggested for administration in many countries. Accordingly, vitamin K supplementation has been recommended to be administered parenterally when there is an indication of the presence of prolonged coagulation secondary to vitamin K deficiency. Cooling effects and moisturizing might also have a potential relieving impact [31].

2. CONCLUSION

The administration of ursodeoxycholic acid has been studied by various studies in the literature, and evidence is conflicting about its potential efficacy and safety. However, recent evidence for a meta-analysis indicates that the modality can reduce pruritis, however, the effect is minimal and insignificant when compared to the placebo group. No significant differences were also noticed between the placebo and treatment groups. We also found that other treatment modalities than ursodeoxycholic acid can also be administered. However, these were not adequately discussed in the literature, and therefore, should be cautiously administered within the clinical settings. Finally, further trials

are needed to validate the current evidence and enhance the quality of reporting and planning proper management guidelines.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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