Received: 2 January 2021 | Revised: 1 April 2021 | Accepted: 6 April 2021

DOI: 10.1111/liv.14913

BRIEF DEFINITIVE REPORT

Liver INTERNATIONAL WILEY

Pregnancy outcome of anti-HCV direct-acting antivirals: Real-life data from an Egyptian cohort

Mohamed AbdAllah[1] | Mohamed Alboraie[2] | Wael Abdel-Razek[3] | Mohamed Hassany[4] | Islam Ammar[5] | Ehab Kamal[1] | Mahmoud Alalfy[6] | Ahmed Okasha[6] | Wafaa El Akel[7] | Elsaied Shaaban[8] | Tamer Elbaz[7] | Zeinab Hefny[9] | Ahmed Gomaa[10] | Mahmoud El-Bendary[11] | Magdy El-Serafy[7] | Gamal Esmat[7] | Wahid Doss[7] | Manal H El-Sayed[12]

[1]Medical Research Division, National Research Center, Cairo, Egypt

[2]Department of Internal Medicine, Al-Azhar University, Cairo, Egypt

[3]Department of Hepatology and Gastroenterology, National Liver Institute, Menoufia University, Menofyia, Egypt

[4]Department of Hepatology, National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt

[5]Department of hepatology, gastroenterology and infectious diseases, Al-Azhar University, Cairo, Egypt

[6]Reproductive health and family planning department, National Research Center, Cairo, Egypt

[7]Department of Endemic Medicine and Hepatology, Cairo University, Cairo, Egypt

[8]Internal medicine department, El-Mataria teaching hospital, Cairo, Egypt

[9]Tropical medicine department, Ain Shams University, Cairo, Egypt

[10]Tropical Medicine Department, Faculty of Medicine, Fayoum University, Fayoum, Egypt

[11]Tropical Medicine and Hepatogastroenterology, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt

[12]Department of Pediatrics and Clinical Research Center, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Correspondence
Mohamed Alboraie, Department of internal medicine, Al-Azhar University, Nasr City, 11884 Cairo, Egypt.
Email: alboraie@azhar.edu.eg

Funding information
None.

Handling Editor: Benjamin Maasoumy

Abstract

We aimed to assess the pregnancy outcome in women with chronic HCV who had negative pregnancy test prior to the anti-HCV course and had unintended pregnancy while on HCV treatment. Hundred patients with a mean age of 30 ± 6.7 y were included and advised to withhold antivirals and continue follow-up in viral hepatitis and obstetrics centres till delivery. All patients received a 12-weeks regimen of anti-HCV [sofosbuvir plus daclatasvir (SOF/DCV): n = 95, SOF/DCV plus ribavirin: n = 3, and paritaprevir/ritonavir/ombitasvir plus ribavirin: n = 2]. Only nine patients completed the full antiviral course against medical advice, and 91 stopped between on-treatment weeks 4 and 8. Eighty-eight patients delivered full-term babies, eight had preterm babies and two had abortions. Of the nine patients who completed the full course of DAAs, seven (77.8%) delivered normal babies, attended their post-treatment week 12 visit, and all (100%) achieved sustained virological response. No major antiviral-related adverse events were reported.

List of Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; DAAs, Direct-acting antivirals; DCV, Daclatasvir; FDA, Food and drug administration; FIB-4, Fibrosis-4 index; HCV, Hepatitis C Virus; INR, international normalized ratio; IQR, interquartile range; OBV/PTV/r, Ombitasvir, paritaprevir, and ritonavir; RBV, Ribavirin; SOF, Sofosbuvir; TGA, Australian Therapeutic Goods Administration.

KEYWORDS

daclatasvir, direct-acting antivirals, hepatitis C, pregnancy, sofosbuvir

1 | INTRODUCTION

Chronic Hepatitis C virus infection (HCV) is a major healthcare problem that affects about 70 million people worldwide.[1] Vertical transmission of HCV can occur in 5%-17% of HCV pregnant women.[2] Direct-acting antivirals (DAAs) are currently the treatment of choice for HCV.[3] In late 2018, Egypt successfully screened about 50 million adults for HCV in a large national screening campaign and treated over 1 million patients. This campaign used a locally manufactured sofosbuvir (SOF) plus daclatasvir (DCV) regimen with or without ribavirin (RBV) as a first line therapy where some DAAs such as Ombitasvir, paritaprevir and ritonavir (OBV/PTV/r) in addition to RBV were used in special situations.[4] Some of these drugs are potentially safe during pregnancy as sofosbuvir, OBV/PTV/r and ledipasvir. They are classified by the food and drug administration (FDA) as pregnancy category B drugs. Meanwhile, ribavirin is classified as category X and daclatasvir is classified as B3 according to the Australian Therapeutic Goods Administration (TGA). Currently, there are no approved regimens of DAAs for treatment of HCV in pregnant women.[5] Few published data denoted safety of some DAA regimens. A study from India reported no adverse events using ledipasvir/sofosbuvir in 15 pregnant HCV-infected females in the second and third trimesters.[6] Another study confirmed no potential adverse fetal outcomes with use of sofosbuvir during pregnancy.[7] In the current study, we aimed to explore the safety of DAAs and pregnancy outcomes in a series of women who had unintended pregnancy while on HCV treatment.

2 | SUBJECTS AND METHODS

In the period between October 2018 and May 2019, this retrospective-prospective study included a total of 341 female patients with chronic HCV who had unintended pregnancy while on HCV treatment or during the pretreatment evaluation. According to the Egyptian HCV management protocol, every female in the childbearing period should undergo a pregnancy test prior to starting treatment. The time interval between the pretreatment evaluation and the commencement of treatment in the Egyptian mass screening program was one week on average. Two hundred and forty-one women (70.67%) were in the pretreatment assessment and subsequently their HCV treatment was postponed. The remaining 100 pregnant females who were taking HCV medications were evaluated by a hepatologist and obstetrician. Patients were advised to stop DAAs and to have regular follow-up visits in the viral hepatitis and obstetrics clinic until delivery. A series of follow-up phone calls, regular follow-up visits which included detailed history for any adverse events, thorough clinical examination, complete blood counts, kidney and liver tests, in addition to prenatal care visits at the obstetrics clinic were conducted. Fibrosis stage was assessed non-invasively using abdominal ultrasound and FIB-4 score.[8] Anatomy scans were scheduled at 18-20 wk of pregnancy. Data of the studied pregnant women were presented as median and interquartile range (difference between 75th and 25th quartile).

3 | RESULTS

3.1 | Baseline characteristics and pretreatment evaluation

This study included 100 consecutive women (mean age of 30 ± 6.7 y) with chronic HCV who had unintended pregnancy while on HCV treatment. They were mainly residents of urban provinces (66%) in Egypt. All patients were treatment-naïve and only 3% had comorbid conditions (diabetes and hypertension). All patients (100%) had HCV mono-infection and one patient only had cirrhosis (Child-Pugh class A). Baseline laboratory investigations for pregnant women who completed DAAs treatment course (n = 9) were: HCV-RNA (median 62.5, IQR 75.6) x10^3 IU/ml, ALT (median 34, IQR 13) IU/l, AFP (median 3.7, IQR 1.5) ng/ml, total bilirubin (median 0.5, IQR 0.4) mg/dl, INR (median 1, IQR 0.3), creatinine (median 0.8, IQR 0.45) mg/dl and FIB-4 (median 0.68, IQR 0.45).

All patients were prescribed 12-weeks DAAs regimens for HCV which included: SOF/DCV in 95 patients (95%), SOF/DCV plus RBV in three patients and OBV/PTV/r plus RBV in two patients. Among the 100 pregnant women, 62 (62%) denied use of any contraceptive method, 19 (19%) used barrier contraception (male condom), 15 (15%) used oral contraceptive pills, 2(2%) used intrauterine contraceptive devices and 2 (2%) used injectable hormonal contraceptives.

3.2 | Outcome in short-course DAA therapy

Ninety-one patients (91%) stopped DAAs between week 4 and week 8 of treatment upon discovery of pregnancy. Pregnancy was diagnosed in 37 patients during the first month of treatment and in 54 during the second month. None of the 52 patients with documented follow-up achieved SVR after 12 wk of treatment. These patients preferred to postpone treatment until the end of the breastfeeding period.

3.3 | Outcome in full-course DAA therapy

Nine patients completed a full course of DAAs despite the medical advice to withhold treatment. None of them were on RBV-containing

DAA regimen. Of those, seven patients delivered normal full-term babies and all achieved SVR while two were lost to follow-up.

3.4 | Anatomy scan results and follow-up

Of the 100 studied pregnant ladies, 22 attended the anatomy scan visits. No anomalies could be detected whether in the anatomy scan or post-delivery among those babies. Neonates of ladies who did not attend the anatomy scan visit (n = 74) were normal at delivery except one who has been diagnosed with an atrial septal defect. Two women were lost to follow-up, and two had abortions in the first and second trimesters. Out of the remaining 96 deliveries, 88 (91.7%) neonates were born full-term and 8 (8.3%) were pre-term. Three patients had postpartum haemorrhage and one neonate developed physiological jaundice. The majority of pregnant women had normal vaginal deliveries (80/96, 83.3%), while 16 (16.6%) had caesarean sections. No major adverse events related to DAAs, liver decompensation, renal impairment, gross fetal anomalies, maternal, fetal or neonatal mortalities were reported (Figure 1). There did not appear to be an association between the pregnancy outcomes and the DAA therapy.

4 | DISCUSSION

Most published data about safety of DAAs during pregnancy and lactation came from animal studies which may not be fully applicable in humans.[7] Few data about safety of DAAs in humans during pregnancy indicated no major fetal outcomes.[9]

To date, two studies with a small number of patients showed no safety concerns for using sofosbuvir during pregnancy and high sustained virological response when using ledipasvir/sofosbuvir.[6,10] Although ribavirin is contraindicated during pregnancy based on animal data showing teratogenic and/or embryocidal effects, none of these effects were reported among the studied cohort of five patients who received ribavirin in combination with SOF/DCV or paritaprevir/ritonavir/ombitasvir. Further human data from pregnancy registries and large HCV treatment cohorts in different parts of the world are required to monitor safety of DAAs.

Majority of the studied women conceded not being compliant to the hepatologist's advice for using two reliable methods of contraception. About 62% of them did not use any contraception and the rest either used hormonal methods or a single barrier contraceptive. The relatively young age, absence of advanced liver disease in most of the studied patients, highly safe, effective and freely available DAAs treatment could explain their reluctance to comply with contraception advice. Additionally, non-compliance to contraception is not always because of female negligence. Some social constraints like husband attitude and request to avoid contraception may be an additive drive for non-adherence to contraception. The current results highlight the importance of enhanced counselling in female patients in childbearing age to use two effective contraceptive methods especially with ribavirin-containing regimens. In our study, nine patients insisted to complete the whole course of treatment with DAAs against medical advice to withhold therapy. This group could have been suffering from HCV stigma which might have affected their social and marital lives and required to achieve cure from HCV infection. HCV related stigma has been indicated to clearly affect young married persons in a recent study from Egypt.[11]

Only one infant was diagnosed with atrial septal defect after delivery, to a mother who did not attend the anatomy scan visit. It is to be noted that the prevalence of neonatal congenital heart disease in Egypt is around 5-6/1000.[12] None of the remaining infants born to mothers who continued follow-up, had any other congenital abnormalities diagnosed through anatomy scans or after delivery. Although only seven pregnant ladies had documented full-term deliveries after a complete course of DAAs (sofosbuvir plus daclatasvir for 12 wk), 37% of the patients had received at least 4 wk of DAAs during the first trimester of pregnancy. This short course of treatment is not enough to prove safety of DAAs in pregnant women, however, it can justify further research. Most of the delivered infants in the current cohort (88%) were full-term suggesting no or low risk of preterm labour associated with the use of DAAs. The rate of preterm labour in our cohort (10%) is similar to the rate reported in a systematic review by the World Health Organization (11.9% preterm labour in African pregnant ladies).[13] The scheduled anatomy scan at 18-20 wk of pregnancy did not reveal any fetal abnormalities in all screened pregnant women. The incidence of congenital malformation according to an Egyptian study was 20/1000.[2]

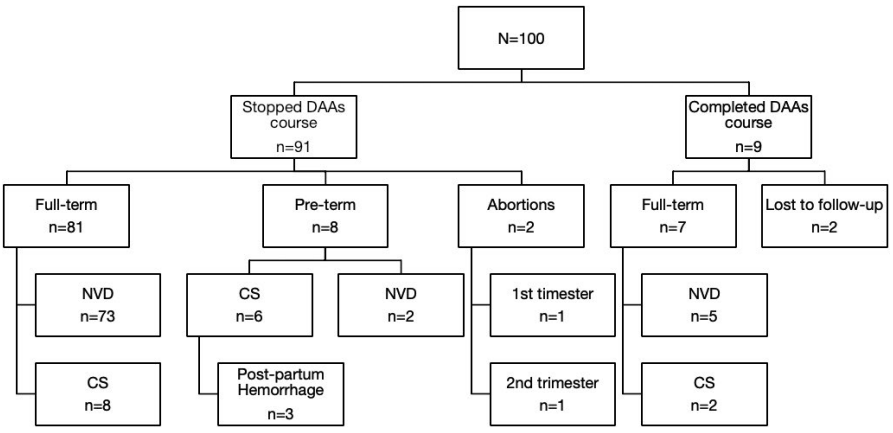

FIGURE 1 Flowchart of the studied pregnant women. CS, cesarean section; DAAs, direct-acting antivirals; NVD, normal vaginal delivery

In our study, there was no increased risk of postpartum maternal or fetal adverse events. Furthermore, there were no other adverse events or systemic affections reported indicating potential safety of DAAs in this special population of pregnant women.

To our knowledge, this is the first report for the accidental exposure to sofosbuvir plus daclatasvir for 12 wk during the first trimester of pregnancy with no reported serious adverse outcomes. Limitations of this study include a small number of enrolled patients and lack of anatomy scan data for majority of patients. This was partly because of geographical constraints preventing access to well-equipped obstetrics clinics and missing follow-up visits after delivery.

In conclusion, in the studied cohort of HCV-infected pregnant women, DAAs were potentially safe without major fetal anomalies or related adverse pregnancy outcomes. These data can inform policies and well-designed clinical trials in HCV-infected women in the second or third trimesters of pregnancy to prevent vertical transmission particularly in resource-limited settings.

CONFLICT OF INTERESTS

Wahid Doss: investigator/speaker: Gilead Sciences. Gamal Esmat: investigator/speaker/advisory board member: Abbvie, Gilead Sciences, Marcyrl, Pharco, Roche. Manal El-Sayed: speaker/podcast: WHA/Abbott, Gilead. All other authors: nothing to be declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Mohamed Alboraie https://orcid.org/0000-0002-8490-9822
Mohamed Hassany https://orcid.org/0000-0002-6001-8793
Ahmed Okasha https://orcid.org/0000-0002-0029-4577
Mahmoud El-Bendary https://orcid.org/0000-0002-3751-5927

REFERENCES

1. Lombardi A, Mondelli MU. ESCMID study group for viral hepatitis (ESGVH). hepatitis C: is eradication possible?. *Liver Int Off J Int Assoc Study Liver*. 2019;39(3):416-426.
2. Elrazek A, Amer M, El-Hawary B, et al. Prediction of HCV vertical transmission: what factors should be optimized using data mining computational analysis. *Liver Int*. 2017;37(4):529-533.
3. Jiménez-Pérez M, González-Grande R, España Contreras P, Pinazo Martínez I, de la Cruz LJ, Olmedo MR. Treatment of chronic hepatitis C with direct-acting antivirals: the role of resistance. *World J Gastroenterol*. 2016;22(29):6573-6581.
4. Waked I, Esmat G, Elsharkawy A, et al. Screening and treatment program to eliminate hepatitis C in Egypt. *N Engl J Med*. 2020;382(12):1166-1174.
5. Ghany MG, Morgan TR. AASLD-IDSA hepatitis C guidance panel. hepatitis C guidance 2019 update: American association for the study of liver diseases-infectious diseases society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Hepatol Baltim Md*. 2020;71(2):686-721.
6. Yattoo G. Treatment of chronic hepatitis C with ledipasvir/sofosbuvir combination during pregnancy [Abstract]. *Hepatol Int*. 2018;12(Suppl. 2):S292-S293.
7. Radovich E, El-Shitany A, Sholkamy H, Benova L. Rising up: fertility trends in Egypt before and after the revolution. *PLoS One*. 2018;13(1):e0190148.
8. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology*. 2007;46(1):32-36.
9. El-Sayed MH, Elakel W, Elsharkawy A, et al. THU-137-DAA therapy in women of child bearing age: accidental conception during therapy and pregnancy outcome. *J Hepatol*. 2019;70(1):e221.
10. Chappell CA, Scarsi KK, Kirby BJ, et al. Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study. *Lancet Microbe*. 2020;1(5):e200-e208.
11. Soltan EM, Salama HM, Aboelmagd MA. Assessment of stigma among patients infected with hepatitis C virus in Suez City. *Egypt. J Public Health*. 2018;26:279-288.
12. Wahba S, El-Sese A, Taha GM, El-Malaah W. Prevalence of congenital heart diseases among neonates with congenital malformations. *Alex J Pediatr*. 2002;16(2):223-227.
13. Beck S, Wojdyla D, Say L, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*. 2010;88(1):31-38.

How to cite this article: AbdAllah M, Alboraie M, Abdel-Razek W, et al. Pregnancy outcome of anti-HCV direct-acting antivirals: Real-life data from an Egyptian cohort. *Liver Int*. 2021;41:1494–1497. https://doi.org/10.1111/liv.14913