Acceptability of hepatitis C screening and treatment during pregnancy in pregnant women in Egypt, Pakistan and Ukraine: a cross sectional survey

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Abbreviations:

DAAs	Direct acting antivirals
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LMIC	Low and middle-income countries
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
VT	Vertical transmission
WHO	World Health Organization

BACKGROUND

Chronic hepatitis C (HCV) in women of childbearing age is a major public health concern with ~15 million women 15–49 years living with HCV globally in 2019.[1] The risk of HCV vertical transmission (VT) is estimated at ~6% and is the leading cause of HCV acquisition in the ~3 million children living with HCV in 2018.[2] Furthermore there is growing evidence of adverse pregnancy and infant outcomes associated with maternal HCV, including preterm birth, low birth weight and intrahepatic cholestasis of pregnancy.[3,4]

The global goal for elimination of viral hepatitis by 2030 requires 90% of all persons living with HCV to be diagnosed and >80% treated and cured with direct acting antivirals (DAAs). However, pregnant and breastfeeding women are currently excluded from HCV elimination strategies; few countries offer free routine antenatal HCV screening,[5] and DAAs are not licensed for pregnant and breastfeeding women. WHO[6] and European[7] guidelines recommend deferring HCV treatment until after delivery and cessation of breastfeeding however recent updates to AASLD/IDSA guidelines in 2022 states use of DAA in pregnancy can be considered on a case by case basis although safety and efficacy data in this population remains scarce.[8] In many low and middle-income countries (LMIC), women breastfeed for ≥2 years and have pregnancies in rapid succession, limiting opportunities for timely treatment. Studies in high-income and LMIC have reported <50% retention in HCV care and low uptake of DAAs post-partum,[4,9] resulting in ongoing risk of HCV disease progression and transmission risks in subsequent pregnancies. These recommendations for deferred treatment for pregnant women with HCV are in contrast to international guidelines for HIV and hepatitis B where antiretroviral therapy during pregnancy is recommended for *all* women with HIV (irrespective of clinical, immunological and virological status) [10] and pregnant women with HBV infection (HBsAg positive) and HBV DNA ≥ 5.3 log10 IU/mL (≥ 200,000 IU/mL) to prevent vertical transmission.[11]

Phase I studies have assessed the pharmacokinetics of DAA sofosbuvir/ledipasvir from 24 weeks (n=8),[9] and sofosbuvir/velpatasvir from 23 weeks gestation (n=11),[12] in pregnant women with HCV. Across the two studies, all but one participant completed 12-weeks treatment, had adequate drug exposure and achieved functional cure by delivery, with no safety concerns. Other small studies on off-label use of DAAs in pregnancy or conception during treatment reported no safety signals.[13,14] To date only one single-site study has examined the acceptability of HCV treatment in pregnancy, surveying 121 non-pregnant women with current/previous HCV in the USA; 60% reported willingness to take DAAs in pregnancy to reduce VT risk, and 21% for maternal cure, even if it did not reduce VT.[15]

We conducted a cross-sectional survey to assess the acceptability of free universal antenatal HCV screening and DAAs use in pregnancy in the scenario that DAAs were shown to be safe for use in pregnancy, in three high HCV burden countries: Egypt, Pakistan and Ukraine. Egypt and Pakistan have generalised HCV epidemics with estimated prevalence in pregnant women of 9%[16] and 6%[17] respectively. Ukraine has a

concentrated HCV epidemic with high prevalence among people living with HIV.[18]

METHODS

All women aged ≥18 years who were pregnant or recently delivered (within 6-months), attending participating antenatal clinics/maternity hospitals in Egypt (1 public hospital), Pakistan (2 public and 5 private hospitals) and Ukraine (3 public, including 1 HIV clinic) were invited to participate, irrespective of their HCV status (n=210 per country). In Egypt and Pakistan, women were randomly selected. The three clinics in Ukraine specialised in infectious disease and the study staff in these clinics targeted women with HCV to ensure they were represented in the sample. The study was approved by local ethics committees, all women gave written informed consent.

A survey was developed in REDCap (www.project-redcap.org) and translated into local languages. Minor local adaptions were made, e.g. HIV status was not collected in Egypt or Pakistan as considered highly sensitive and both countries have low HIV prevalence and no routine antenatal HIV testing. The survey ran from July 2020 to July 2021.

The survey collected data on socio-demographic, pregnancy status, self-reported HCV status and HCV knowledge. Participants were then given a factsheet about HCV and pregnancy, adapted from Kushner et al,[15] and asked their views on acceptability of antenatal HCV screening and use of DAAs in pregnancy, in the scenario that DAAs were shown to be safe for use in pregnancy. Descriptive statistics summarised participant characteristics and survey responses, overall and by country, HCV and HIV status.

RESULTS

Of the 630 participants median age was 30 [IQR 26,35] years (Table 1). In Egypt, 52 (25%) of women were never tested for HCV compared to 21 (10%) in Pakistan and 14 (7%) in Ukraine. Over half of women in Ukraine (n=123) were ever HCV positive (antibody or RNA) versus 7 (3%) and 42 (20%) in Egypt and Pakistan, respectively. In Ukraine, 83 (40%) women were living with HIV, of whom 27 (33%) were ever HCV positive.

Overall, 586 (93%) reported acceptability of universal antenatal HCV screening and 554 (88%) would take DAAs in pregnancy; DAA acceptability was highest in Pakistan (n=206 (98%)) followed by Egypt (n=191 (91%)) and Ukraine (n=153 (73%)) (Figure 1). The majority of women would take DAAs in pregnancy to prevent VT and other potential benefits to the baby (n=100 (48%) in Ukraine, n=132 (63%) in Egypt and n=189 (90%) in Pakistan). A smaller proportion (8-29%) would take DAAs for maternal cure. Acceptability was highest among HCV negative women (n=229 (92%)) compared to n=173 (78%) in women who ever tested HCV positive. In Ukraine, acceptability was similar irrespective of HIV status.

DISCUSSION

To our knowledge, this is the largest study to date on acceptability of HCV screening and treatment in pregnant/post-partum women and the first in high burden LMICs. Acceptability of antenatal HCV screening was extremely high at 93%. In the scenario that DAAs were shown to be safe for use in pregnancy, acceptability ranged from 78% in Ukraine to 98% in Pakistan. These estimates are markedly higher than the 60% acceptability reported in the USA.[13] The difference may be due to our study including women currently pregnant/recently delivered and women with known and unknown HCV status. As with the USA study, most women would take DAAs primarily to prevent VT and adverse pregnancy/infant outcomes.

Strengths of our study are the inclusion of women across three countries, in public and private clinics and an HIV clinic. One limitation is that acceptability was based on a scenario that woman had chronic HCV, and that DAAs were shown to be safe for use in pregnancy. Most women in Pakistan and Egypt were HCV negative or had never tested. However almost 60% of women in Ukraine were ever HCV positive, this high prevalence reflects the selected clinics being specialized in infectious diseases and targeted enrolment of women with HCV in these sites, leading to an over-estimate of the prevalence in this setting. However the over-sampling of women with HCV was important to show that within the subgroup acceptability of DAAs was similarly high at 88%.

Free universal antenatal HCV screening is only recommended in few, mostly high-income countries, however this is not yet recommended in the WHO guidelines nor in most high burden countries where only 'high risk' groups are screened or screening incurs an out of pocket cost. There are currently no recommendations promoting HCV treatment of pregnant women with chronic HCV due to lack of data on safety and effectiveness. Deferring treatment until after delivery and end of breastfeeding can result in long delays, increasing the maternal risk of disease progression, risk of VT and potential adverse maternal and infant outcomes associated with HCV in their current and future pregnancies. Our study suggests potentially high acceptability of DAA if shown to be safe for use in pregnancy and shown to reduce some of these maternal/infant risks. Indeed there have been reports of pregnant women who in discussion with their care providers have chosen to initiate off-label treatment during pregnancy, despite the limited safety data.[13] Recognizing the importance of such real-world data, the Coalition for Global Hepatitis Elimination (CGHE) has established an online 'Treatment In Pregnancy for Hepatitis C': The TiP-HepC Registry[19] to encourage reporting of data on use of DAAs in pregnancy, which will be crucial in consolidating emerging data on the safety of DAAs in this population. Nonetheless, clinical trials on the safety and efficacy of DAAs in pregnancy and breastfeeding period are urgently needed to inform future care and policy to ensure that pregnant women with HCV and their children do not continue to be left behind in the global elimination effort.

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Table 1 Sociodemographic characteristics of participants by country

		Egypt (n=210)	Pakistan (n=210)	Ukraine (n=210)	Total (n=630)
		n (%) or median [IQR]			
Age (years)		30 [26,34]	29 [26,33]	33 [28,36]	30 [26,35]
Age group (years)	18-24	42 (20)	29 (14)	27 (13)	98 (16)
	25-34	117 (56)	150 (71)	105 (50)	372 (59)
	≥35	51 (24)	31 (15)	78 (38)	160 (25)
HCV status (self-report)	Ever HCV positive (antibody or RNA)	7 (3)	42 (20)	123 (59)	172 (27)
	HCV negative	150 (71)	147 (70)	72 (34)	369 (59)
	Never tested	53 (25)	21 (10)	15 (7)	89 (14)
HIV status (self-report)	HIV positive	-	-	83 (40)	83 (13)
	HIV negative	-	-	126 (60)	126 (20)
Pregnancy status	Gave birth in last 6 months	75 (36)	78 (37)	14 (7)	167 (27)
	Currently pregnant	135 (64)	132 (63)	196 (93)	463 (73)
Parity	First pregnancy	35 (17)	40 (19)	81 (39)	156 (25)
	Previous pregnancy	175 (83)	170 (81)	129 (61)	474 (75)
Number of previous children (not including recent/current pregnancy)		2 [1,3]	2 [1,3]	1 [1,2]	2 [1,3]
Relationship status	Divorced, separated, widowed, single	0 (0)	0 (0)	23 (11)	23 (4)
	Married, co-habiting	210 (100)	210 (100)	186 (89)	606 (96)
Highest level of education	Less than secondary	89 (42)	85 (40)	19 (9)	193 (31)
	Completed secondary school/college	81 (39)	39 (19)	110 (52)	230 (37)
	University or higher	40 (19)	86 (41)	81 (39)	207 (33)
Overcrowding score †		1.5 [1.0,2.0]	1.8 [1.3,2.7]	1.0 [1.0,1.7]	1.5 [1.0,2.0]

Employment status	Full-time or student	22 (10)	35 (17)	71 (34)	128 (20)
	Part-time	13 (6)	22 (10)	39 (19)	74 (12)
	Unemployed/other	175 (83)	153 (73)	100 (47)	428 (68)
Partner's employment status	Full-time or student	98 (47)	159 (76)	145 (69)	402 (64)
	Part-time	95 (45)	40 (19)	38 (18)	173 (27)
	Unemployed/other	17 (8)	11 (5)	4 (2)	32 (5)
	N/A (no partner)	0 (0)	0 (0)	23 (11)	23 (4)
Ever heard of HCV	No	27 (13)	5 (2)	7 (3)	39 (6)
	Yes	183 (87)	205 (98)	202 (97)	590 (94)
HCV Knowledge Score ‡		11 [8,14]	11 [9,14]	14 [13,17]	12 [9,15]

†Overcrowding score is number of people in home/ number of rooms (excluding kitchen and bathroom)

‡ HCV knowledge score was derived from allocating a point for each HCV knowledge question correctly answered, max score 24

Abbreviations: HCV - Hepatitis C virus; HIV - Human immunodeficiency virus; IQR – interquartile range; RNA - Ribonucleic acid

Note: all variables included in this table had p value for comparison between countries <0.01