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Advances in HCV Treatment-Effect of HCV Infection/HCV Treatment (PEG-IFN/Ribavirin) on Fertility (Ovarian Reserve) - A Case Report

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Abstract

Hepatists C Virus is a RNA virus belonging to the Fl avirividae family. It has been seen in previous studies that HCV infection perse is associated with reduced ovarian reserve and higher cycle cancellation rate in ovarian cycles. Simultaneously treatment of HCV with Pegylated Interferon (PEG-IFN) and ribavirin (RBV) is known to affect the ovarian reserve. Although there are some controversial reports regarding effect of HCV on fertility. Some guidelines have been laid regarding on co-fertility situations where prior to starting treatment cryopreservation of oocytes/embryos should be done by doing an IVF cycle. We discuss such controversial issues in a case who had chronic HCV infection affecting liver function besides bad obstetric disease and needed antiviral therapy for Chronic HCV infection affecting liver function, but whether at her age was doing cryopreservation indicated or justified in view of her age and known effects of HCV treatment on future fertility and risk of spread. We also review the modern advancements in the treatment of HCV infection and their future effects on fertility.

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Introduction

Hepatitis C Virus (HCV) is a small enveloped, single stranded RNA virus of the Flavirividae family[1]. First cloned by Choo *et al* in 1989[2], HCV is an important global[3], chronic viral disease which mainly affects the liver. Rate of progression is individualized, where some patients can recover completely, while others would like to have children with disease[4-6]. Most HCV serodiscordant couples conceive children normally, but some are infertile and thus may need ART. ART in these patients has been controversial, with attitudes of IVF centres differing in different countries. Besides the ethical dilemma of offering infertility treatment to the patients at risk of nosocomial and professional transmission during the highly complex IVF procedure need to be taken into account[7,8]. Englert *et al* studied the impact of seropositivity with HCV virus on IVF outcome in a retrospective study, where they found a statistically significantly absence of ovarian response in HCV seropositive women as compared with controls 10/42 *vs.* 5/84 cycles, respectively. For cycles with oocyte retrieval HCV seropositive women required more gonadotropin units as compared to controls. HCV positive women had statistically significant fewer embryos available as compared to controls. Thus they concluded when compared with matched uninfected controls, HCV seropositive women display decreased

ovarian response[9]. The reasons for the higher proportion of cancelled cycles for HCV positive women are unknown. Factors known to induce poor ovarian response like maternal age or tubal disease were similar compared with controls. One attributes the poor ovarian response to reduced ovarian reserve. Chronic infection could change the reserve of small preantral follicles and granulosa cell function which leads to increased FSH needed during ART[9]. Chronic HCV infection has been associated with many cellular disorders. This infection is characterized by a circulating viral load in peripheral blood and has been linked to both hepatic and non hepatic diseases like arthritis, glomerulonephritis, or other autoimmune diseases[10,11]. *In vitro* study of HCV antigens and or with HCV subgenomic systems have shown that the products encoded in the HCV genome could interfere with and disturb intracellular transduction and phosphorylation processes[11]. With the microarray analysis HCV infected cells have been shown to have increased activity of the genes participating in immune response, fibrosis, cellular proliferation and apoptosis[12]. The HCV core protein acts as a positive regulator of FAS mediated apoptosis in Peripheral Blood Mononuclear Cells (PBMC) interferes with cellular transduction pathways, leading to inhibition of cell proliferation or an increased level of apoptosis[13,14].

Mechanism by which virus enters the cell is not known. There is a possible role for low density lipoproteins receptors as HCV receptors have been suggested. LDL receptors are present on granulose cells, where they are up regulated by GnRH agonists, human FSH, or HCG[15,16]. Maturing follicles are in close contact with peripheral blood, suggesting granulosa cells come in contact with circulating HCV, which could lead to attachment of HCV to LDL receptors ≥ induction of apoptosis mechanism. A lower level of apoptosis in granulosa cells is associated with better outcomes for human oocytes with a higher embryo quality; with a greater correlation of pregnancy rates with lower rates of apoptosis[17,18]. In a study of 6 HCV In women higher granulosa cell apoptosis was reported as compared to controls[18].

To study the effects of HCV antiviral therapy on ovarian reserve Midan *et al* carried out a prospective longitudinal study where they examined 50 patients receiving either pegylated interferon [PEG IFNα2a or PEGIFNα2b plus ribavirin for a total of 48 weeks. AMH was done in all patients before start of treatment (mean 1 - 3 ng/ml and at the end of treatment program. Additionally they examined ovarian volume by ultrasound. At the end of treatment 28% of studied cases remained in pretreatment level of AMH, in 32% of studied cases AMH decreased, whereas in 40% of cases it increased. Thus they concluded that the IFN and ribavirin affect ovarian reserve in treated patients as in 72% of patients change of AMH levels occurred[19].

Recently Yang *et al* studied 1424 couples with 90 couples where female was HCV positive,78 where male was HCV positive and 1256 couples as controls with both partners HCV negative. They did not find any difference in outcome regarding ovarian stimulation, fertilization and pregnancy results[20].

Till 2001 - 2011 common treatment for chronic HCV infection was a combination of PEG-IFN and ribavirin (RBV). L unah *et al* reviewed the newer oral antiviral drugs like Blocepravir and teltapravir 2 first generation N53/4 a protease inhibitor and sinepravir, approved in combination with PEG-IFN and RBV for 24 - 48 wks in HCV genotype 1infections in may 2011and 2013 respectively[21].

Further one has to wait for the effect of these drugs on fertility. Pregnancy, occurring spontaneously following PEG-IFN-RBV has been reported[22]. We report a 40 yr old patient who presented with history of BOH and had chronic HCV infection requiring antiviral treatment and needed fertility. The effect on her fertility is discussed and if cryopreservation was indicated or justified.

Case Report

A 40 year old patient presented with secondary infertility of 4 years in 2013. She had regular cycles every 30 days lasting 3 - 4 day. Her weight was 49 kg, ht-153, BMI-29.96 kg/m^2, BP was 160/90 mmHg. She had previous 2 spontaneous abortions one at 31/2 months where she had expelled a fetus although no D & C was required. Subsequently she had a pregnancy of 2 months with positive UPT and she got bleeding although USG was not done.

Her mother was a diabetic on oral anti diabetic treatment.

On routine testing for viral profiles although HIV and HBsAG was negative she had a positive HCV, which was confirmed by anti HCV antibody 13.39 (< 1.03-nonreactive, ≥ 1.05 sco reactive) LFT showed normal SB, her alanine transferases were mildly raised SGOT/PT-44/50, HCV RNA-35*10^5

Fibro scan on initial LSM was 163 (increased), with liver biopsy revealing chronic HCV 5 SCORE 3, fibrosis stage 2.

Because of which she opted for treatment for that from a hepatologist in PGI Chandigarh where she received Pegliton 80mg/wk and ribavirin 200 mg bd x 1 yr and a total of 48 injections of pegliton. Since ribavirin is known to be teratogenic she was not taken up for fertility treatment. Although it is well known that ovarian reserve is low and dose of gonadotropins required is very high normally in IVF /ICSI in such patients this patient needed earlier IVF but since she opted for getting HCV treatment before any fertility options, when her HCV RNA became < 15 by Taqman with normal LFT. Unfortunately by the time she reported back on 18/12/2015 her FSH and LH had increased to 28.27 miu/ml(1.4 - 12.5), LH 12.67(0.4 - 12iu.ml), S. AMH was low 0.12 and since she wanted to confirm with ovarian stimulation as she could not afford donor egg ivf we tried FSH x9 Days but no DF formed. Problem in such patients is as she had initially come at age 40 with a BOH whether cryopreservation of oocytes should be tried in a patient positive for HCV since ovarian reserve is known to decrease with HCV.

Discussion

This patient was a case of BOH and already she had reached age 40 along with being a high risk patient for developing cirrhosis and HCC, in view of high HCV viral count and fibrosis on liver biopsy. Although some criteria have been laid for oocyte /embryo cryopreservation[23], the safety for GA is not known in such a patient with altered liver transaminases along with high viral load. As Is known in previous studies ovarian reserve drops with PEG –IFN with RBV, as checked by AMH and ovarian volume studies the only option left is trying a course of DHEAS course[24] which we have started as she cannot afford donor egg ivf.

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