

# Prevalence of HBsAg and HCV antibodies in a cohort of pregnant women: the continuous survey as public health tool against pregnant and neonatal complications

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## SUMMARY

Pregnancy is a very delicate condition and different external factors can alter fetal development. Microorganisms are surely the principal ones. Several studies have shown that HBV and HCV infections could have an impact on pregnancy outcome.

We performed a survey of blood samples from pregnant women in order to evaluate the presence of HBsAg and HCV antibodies.

6,896 women were tested from 2016 to 2019. 0.2% of the women in the Italian group and 2.1% among the foreigners tested positive for HBsAg, while 0.2% among the Italians and 0.7% among the foreigners were positive for HCV antibodies. Moreover, an increasing trend for both infections was observed in the foreigners.

The results showed that in Italian women the positivity rates for HBV and HCV infections are very low despite the presence of both infections. A different consideration must be made for the foreigners, in whom we observed a higher positivity rate for both infections.

Our findings stress the importance of a continuous surveillance of HBV and HCV markers during pregnancy and suggest that there is still much to be done in order to reduce the risk of these infections in this delicate period of a woman's life.

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## INTRODUCTION

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) are one of the most relevant public health concerns worldwide. With about 2 billion HBV-infected people, approximately 257 million people suffer from chronic HBV infection, of which it is estimated that only 10% are aware of their carrier status. The prevalence of HBV infection varies widely, with the majority of HBV-infected people living in Asia and Africa (World Health Organization, 2020a). In Europe, according to the European Center for Disease Prevention and Control (ECDC), 24,588 cases of hepatitis B were reported in 2018, with an overall male-to-female ratio of 1.5:1. The incidence was 6.0 per 100,000 inhabitants, of which 11% were acute infections, 56% chronic infections, and 33% "unknown".

The most affected age group was 25-34 (European Center for Disease Control and Prevention, 2020). In Italy, 197 new cases of acute HBV infection were reported in 2019, with an incidence of 0.4 per 100,000 inhabitants, unchanged compared to 2018. The most affected age group remains that of 35-54, in which the incidence reaches a value of 0.7 per 100,000 (Epicentro, 2020). The infection affected women in 25.4% of cases.

According to the WHO, around 71 million people worldwide are chronic carriers of HCV. The areas with the highest rates of infection are the WHO Eastern Mediterranean Region and the WHO European Region (2.3% and 1.5%, respectively) (World Health Organization, 2020b). As reported by the ECDC, 37,527 cases of hepatitis C were reported in Europe in 2018, with an incidence of 8.8 cases per 100,000 inhabitants, of which 4% were acute infections, 26% chronic infections and 67% "unknown." The infection was more common among men than women, with a male-to-female ratio of 2.1:1. The most affected age group among males was 35-44 (27 cases per 100,000 inhabitants) while the age group among women was 25-34 (10 per 100,000 inhabitants) (Eu-

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ropean Center for Disease Control and Prevention, 2020). In Italy, 40 new cases of acute HCV infection were reported in 2019, with an incidence of 0.1 cases per 100,000 inhabitants, unchanged compared to 2018 and halved compared to 2009. Although in absolute terms, the largest number of cases was in the age group 35-54, by analyzing the curves with the trend of incidences it can be seen that the highest incidences are found in the age groups 15-24 and 25-34 (Epicentro, 2020).

In Europe, the burden of HBV infections among pregnant women varies among countries, ranging from 0.1% in Norway and Spain to 0.8% in France and Italy, while for HCV the percentages were 0.2% in Spain, 0.4% in Italy, 0.8 in France and 0.9% in Norway (Hofstraat *et al.*, 2017). Sero-prevalence is different among pregnant migrant women. In general, the prevalence of HBV and HCV in migrants, in relation to the overall number of chronically-infected cases, was estimated to be around 25% and 14% respectively, with wide variation in the different countries. Specifically, in western and northern European countries, the relative burden among migrants is higher than that reported in southern and eastern European countries (European Centre for Disease Prevention and Control 2016).

Pregnancy is a very delicate condition, especially during the first three months, when embryogenesis process takes place. In this period, many external risk factors can act to alter the delicate equilibrium that leads to fetal development (La Fauci *et al.*, 2020). Among these factors, microorganisms belonging to the so-called TORCH group are surely the principal ones. In this group, viruses are the most numerous components. For this reasons, viral detections including Rubella, HBV, HCV and HIV antibody searches are routinely performed during pregnancy (Ministero della Salute, 1998). Specifically, Rubella has long been considered an important TORCH agent, able to induce serious fetal malformations and even death (Yazigi *et al.*, 2017). Previous studies have focused on the anti-Rubella antibody status of pregnant women in order to quantify the potential risk of developing pregnancy complications (Calimeri *et al.*, 2012; Lo Giudice *et al.*, 2014) and on unconventional agents, including Hepatitis E virus (HEV), whose research has not yet become routine (La Fauci *et al.*, 2017). Moreover, the management of viral hepatitis in the setting of pregnancy requires special consideration. The primary risks for HBV and HCV during pregnancy are related to the severity of the maternal liver disease and the risk of mother-to-child transmission (MTCT) (Terrault *et al.*, 2021). Many HBV- and HCV-infected women are in their fertile age and consequently their pregnancies might be affected. Several studies have shown that HBV and HCV infections could have a direct impact on pregnancy outcomes, being able to increase the risk for

preterm labor and birth, low birth weight (<2500 g), premature rupture of membranes, gestational diabetes, antepartum hemorrhage, pregnancy-induced hypertension and congenital abnormalities (fetal macrosomia) (Tse *et al.*, 2005; Berkley *et al.*, 2008; Pergam *et al.*, 2008; Reddick *et al.*, 2011; Connel *et al.*, 2011; Lao *et al.*, 2012; Lao *et al.*, 2013; Chen *et al.*, 2016; Zhao *et al.*, 2017; Supriya *et al.*, 2017). However, the mechanisms at the base of these outcomes have not been yet clarified. HBV and HCV do not have a cytopathogenic effect, but both can stimulate intense inflammatory responses in hosts (Piconese *et al.*, 2018). Moreover, despite the fact that they are unable to cross the placental barrier, the elicited inflammation may negatively affect the pregnancy (Tang *et al.*, 2014). Previous studies report negative pregnancy outcomes both in high- and in low-endemic countries in women affected by HBV and HCV infections. Reddick *et al.* (2011) found a high risk of low birth weight in infants of HBV-positive mothers. Moreover, studies reported a high risk of developing gestational diabetes and malformations in HBV-infected women (Safir *et al.*, 2010; Sirilert *et al.*, 2014; Lao *et al.*, 2018; Peng *et al.*, 2019). HCV has been linked to negative pregnancy outcomes, such as increased risk for gestational hypertension, preterm birth and low birth weight (Safir *et al.*, 2010; Connel *et al.*, 2011).

The above findings on pregnancy outcome in patients affected by HBV and HCV infections suggest the importance of antenatal screening during pregnancy. We conducted a serological survey on blood samples from pregnant women collected during routine pregnancy screening in order to evaluate the rate of HBsAg and HCV antibody carriers in a low-endemic territory.

## MATERIALS AND METHODS

### *Samples*

We carried out a serological survey on blood samples from pregnant women in the period 2016-2019 sent to the Virology Laboratory of the University Hospital of Messina, Italy, and collected from pregnant women by the Obstetrics and Gynecology Operative Unit of this health structure during routine blood analysis. Specifically, we searched for HBsAg and HCV total antibodies in order to evaluate the infection by HBV and HCV, respectively.

### *Serological analysis*

The blood samples were centrifuged at 4,000 rpm for 10 minutes in order to obtain the serum. For the quantitative detection of HBsAg a direct "sandwich" test with two incubations, based on the chemiluminescent assay (CLIA) (LIAISON XL MUREX HBsAg Quant, DiaSorin, UK) was used. This is a fully monoclonal-based assay for the quantitative determination of HBsAg in human serum or plasma samples

using Mouse Monoclonal Antibodies against highly conserved epitope of the inner region of HBsAg. The positivity range is 0.050-150 IU/ml.

For the qualitative determination of specific IgG antibodies anti-HCV, an indirect in vitro chemiluminescent immunoassay (CLIA) (LIAISON XL MUREX HCV Ab, DiaSorin, UK) using two recombinant HCV antigens (core and NS4) coating magnetic particles (solid phase), and a third ready to use aqueous HCV antigen (biotinylated NS3), was used. The cut-off discriminating between the presence and absence of HCV Ab has an S/CO value of 1.0.

### Statistical analysis

Descriptive statistics were used to find the percentages and the 95% Confidence Interval (CI). Correlations were determined using either the standard Pearson correlation coefficient or the Spearman's rank correlation test, whereas chi-square was used to compare the observed frequencies. Significance was assessed at  $p < 0.05$  levels. All analyses were performed using Prism 4.0 software.

## RESULTS

From 2016 to 2019, 6,896 blood samples were sent to the laboratory, of which 6,169 (89.4%) were from

Italian and 727 (10.6%) from foreign women. The average age of the pregnant women was  $32.0 \pm 6.0$  y/o in Italians and  $30.9 \pm 6.3$  y/o in foreigners. In total, 15 (0.2%) women in the Italian group and 15 (2.1%) women in the foreign group were positive for HBsAg ( $P < 0.0001$ ), while 13 (0.2%) Italians and 5 (0.7%) foreigners were positive for HCV antibodies ( $P < 0.05$ ). Table 1 shows the details of the performed analysis and the number of positive samples per year.

Figure 1 shows the trend of HBsAg positivity from 2016 to 2019 in the two groups of tested women. Specifically, the positivity percentage  $> 150$  IU/ml was 56.3% in Italians and 75.0% in foreigners.

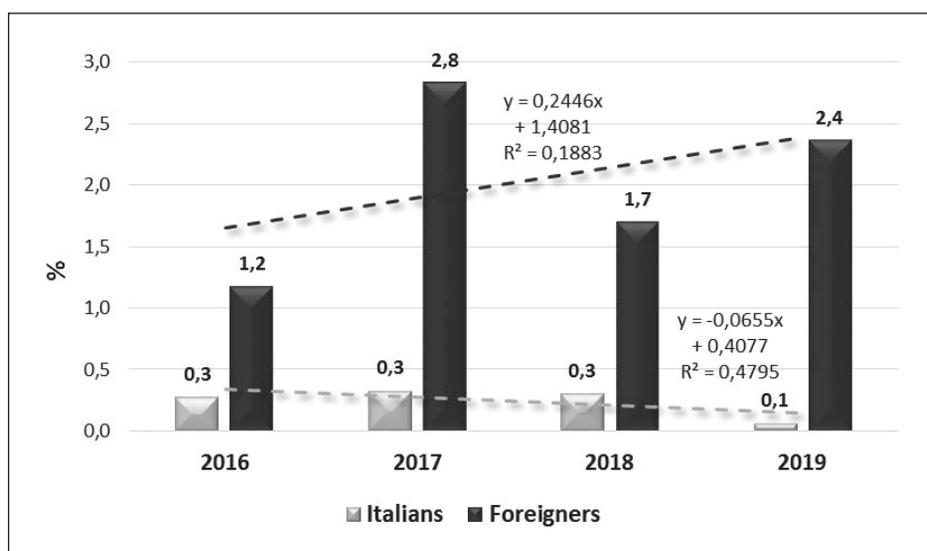
Similarly, Figure 2 shows the trend of HCV positivity in the same period in the two groups of tested women and highlights a statistically significant increase in HCV positivity in foreign pregnant women from 2016 to 2019 ( $P < 0.05$ ). Specifically, the mean values of HCV positivity were  $4.1 \pm 4.3$  in Italians and  $4.8 \pm 4.2$  in foreigners.

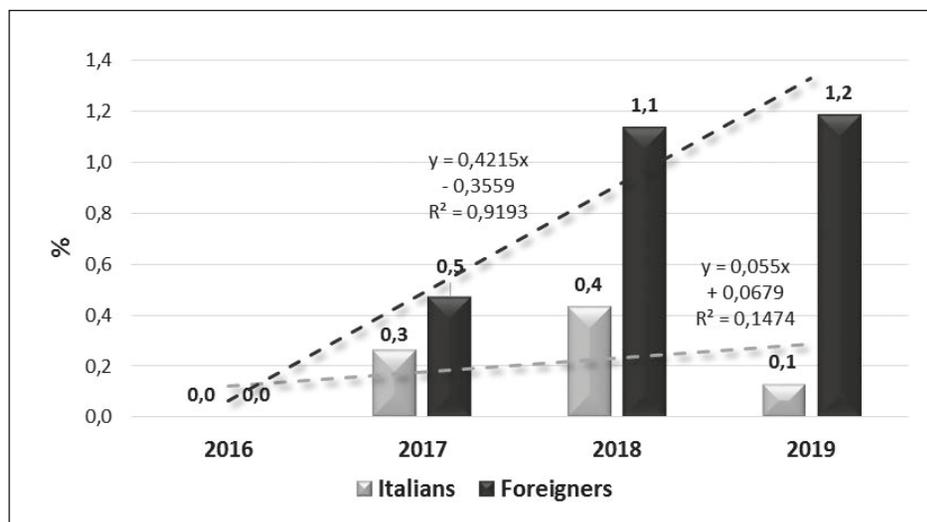
Regarding the women positive for both HBsAg and HCV, we observed a mean age higher than that of the negative ones in both groups. Specifically, in the Italian group, for HBsAg, the mean age of the positive women was  $35.0 \pm 4.0$  versus  $32.0 \pm 6.0$  in the negative ones while, for HCV, the mean age of the positive women was  $33.0 \pm 6.4$  versus  $32.0 \pm 6.0$  in the negative

**Table 1** - Details of the performed analysis and the number of positive samples per each year.

	ITALIANS				FOREIGNERS			
	Number	Mean Age (min-max)	HBsAg positive	HCV positive	Number	Mean Age (min-max)	HBsAg positive	HCV positive
2016	1,454 (23.6%)	31.7 (16-43)	4 (0.3%)	0 (0.0%)	170 (23.4%)	30,6 (17-42)	2 (1.2%)	0 (0.0%)
2017	1,520 (24.6%)	31.9 (14-44)	5 (0.3%)	4 (0.3%)	212 (29.2%)	30,6 (14-43)	6 (2.8%)	1 (0.5%)
2018	1,624 (26.3%)	32.2 (15-45)	5 (0.3%)	7 (0.4%)	176 (24.2%)	32,0 (17-44)	3 (1.7%)	2 (1.1%)
2019	1,571 (25.5%)	32.4 (15-46)	1 (0.1%)	2 (0.1%)	169 (23.2%)	30,6 (16-44)	4 (2.4%)	2 (1.2%)
TOT	6,169		15 (0.2%)	13 (0.2%)	727		15 (2.0%)	5 (0.7%)

**Figure 1** - Trend of HBsAg positivity from 2016 to 2019 in the two groups of studied women.





**Figure 2** - Trend of HCV positivity in the same period in the two groups of studied women.

**Table 2** - Absolute numbers and percentages related to origin of foreign pregnant women.

	HBsAg (%)	HCV (%)
Africa	4 (26.7)	0
India and South East Asia	4 (26.7)	2 (40.0)
Eastern Europe	7 (46.6)	2 (40.0)
Latin America	0	1 (20.0)

ones. In the foreign group, the mean age of the HBsAg positive women was  $33.4 \pm 5.0$  versus  $30.9 \pm 6.3$  in the negative ones while for HCV the mean age of the positive women was  $30.4 \pm 4.3$  versus  $30.9 \pm 6.3$  in the negative ones.

Table 2 shows the absolute numbers and percentages related to the origin of the foreign pregnant women who tested positive for both HBsAg and HCV antibodies.

## DISCUSSION

HBV and HCV infections are still important public health issues in many parts of the world despite the availability of an effective vaccine against HBV and novel therapeutic regimens for the treatment of HCV infection. These two viruses have several similarities, such as the same target cells and disease progression but, on the other hand, differ with regard to the symptoms they determine, the immune response they elicit, and the strategies they use to persist in the host cells. For example, HCV often determines subclinical infections with an important innate immune activation, while HBV typically causes more acute infections but with less propensity to cause chronic hepatic damage than does HCV, especially if contracted in adult life. Moreover, HBV generally involves the innate immune system and to a lesser extent the associated inflammatory response (Ortega-Prieto *et al.*, 2017), while HCV determines sever-

al extrahepatic manifestations such as thyroiditis, insulin resistance and diabetes and autoimmunity (Antonelli *et al.*, 2006; Bugianesi *et al.*, 2012; Flores-Chávez *et al.*, 2017). Finally, the immune response to chronic HCV infection is associated with increased levels of interferon and pro-inflammatory cytokines, determining the activation of different signal transduction pathways and the production of several kinds of proteins potentially able to cross the placental barrier (Fensterl *et al.*, 2015). All these pathogenic conditions are associated with elevated risk of poor perinatal outcomes, such as low birth weight, in mothers affected by chronic HCV infection (Safir *et al.*, 2010; Spiegel *et al.*, 2018).

Previous studies have shown that HBV infection acquired in early pregnancy can make women more susceptible to abortion than those with no infection (Hsu *et al.*, 2012; Supriya *et al.*, 2017). Moreover, if contracted during middle and later pregnancy, damage to liver cells and functions makes these patients more vulnerable to premature delivery and postpartum hemorrhage than those with no infection (Jinjvadia *et al.*, 2014; Chen *et al.*, 2016). Hepatic dysfunction affects the synthesis of albumin and coagulation factors, which determine the accumulation of humors in the tissue space, retention of water and sodium, and hypertension (Kumada *et al.*, 2010; Wang *et al.*, 2010). In addition, the accumulation of HBV-DNA in placenta and trophoblast cells activates the placental inflammatory response and reduces trophoblasts and placental function playing a role in the link between HBV infection and preterm labor (Bai *et al.*, 2007; Elefsiniotis *et al.*, 2011).

In light of these considerations, the prevention of MTCT is a crucial issue. Particularly, the risk of MTCT of HBV is present especially in mothers with high levels of HBV-DNA (HBV-DNA > 200.000 UI/ml) and with HBeAg-positivity, but this risk can be reduced with the use of maternal antiviral therapy and

prompt administration of infant immunoprophylaxis (Terrault *et al.*, 2021). Specifically, newborns from HBsAg-positive mothers have to receive anti-HBV immunoglobulins and the first dose of vaccination within the first 24/48 h of life in order to prevent HBV infection (Ministero della Salute, 2000; EASL 2017; WHO, 2020c). Some previous studies showed that a high maternal anti-HBc level may be a predictor of immunoprophylaxis failure in high-risk infants. Specifically, with HBV-DNA levels <6 log<sub>10</sub> copies/mL, 6-6.99 log<sub>10</sub> copies/mL, 7-7.99 log<sub>10</sub> copies/mL, and >8 log<sub>10</sub> copies/mL, the corresponding rates of immunoprophylaxis failure were 0%, 3.2%, 6.7%, and 7.6%, respectively (Singh *et al.*, 2011; Zhou *et al.*, 2012). Pregnant women with chronic HCV infection have increased rates of adverse pregnancy outcomes; MTCT occurs in 5% and is linked with invasive fetal monitoring and prolonged rupture of membranes (Terrault *et al.*, 2021).

In our study, the sample consisted primarily of Italian women in their thirties. In this group, the positivity for HBV and HCV infection was 0.2% for both conditions. Specifically, for HBsAg positivity, we observed a stable trend from 2016 to 2018, with a percentage of 0.3%, and a clear reduction in the last year of the study, with a very small percentage of 0.1%. On the contrary, HCV-positivity was more irregular because after an increase from 2016 (when no case was detected) to 2018 (with values of 0.3% in 2017 and 0.4% in 2018), we saw a decrease in the last year, with a value of 0.1%. Moreover, in both the groups, the mean age of the positive women was higher than that in the negative ones. This is true especially for Italian HBsAg-positive women in whom we found a significant difference of 3 years in the mean age compared to that in the negative ones. This finding can be partially explained by considering that HBV vaccination became mandatory in Italy for all newborns starting in 1991, with the law 27 May 1991, no. 165 (Gazzetta Ufficiale della Repubblica Italiana, 1991a; Di Pietro *et al.*, 2019). Even if the strategy to undergo vaccination, especially at school, including for twelve-year-olds for the first twelve years after the beginning of the mandatory vaccination was applied in order to cover all the subjects born since 1979 (Gazzetta Ufficiale della Repubblica Italiana, 1991b), it is probable that a certain number of such individuals escaped from the program.

This study shows that the screening carried out in pregnancy is an important epidemiological tool for the monitoring of certain infectious diseases and their circulation among the population. From the analysis of the data obtained by the screening, we showed that in Italian pregnant women, the positivity rates for HBV and HCV infections in our territory are very low, in line with previous surveys. Specifically, Lembo *et al.* found a prevalence of HBsAg and HCV of 0.4% and 0.2%, respectively, in the same

territory (Lembo *et al.*, 2017). Moreover, Spada *et al.* found a percentage of HBsAg of 0.4% in Italian pregnant women compared to those born in Eastern Europe, Asia and Africa, who had percentages of 3.44%, 2.68% and 2.56%, respectively (Spada *et al.*, 2011). Especially for HCV, the prevalence has significantly decreased over time in the entire Italian population, including the previously hyperendemic regions of the South (Guadagnino *et al.*, 2013). In particular, a previous study showed that the current HCV prevalence in women < 40 years old living in a large metropolitan area of southern Italy is 0.4% (Morisco *et al.*, 2017). These findings show the efficacy of the vaccination strategies used to contain the HBV infection and of the rigorous control measures implemented to reduce iatrogenic transmission of HCV. However, both infections are still present and this issue is unacceptable, given the availability of effective preventive measures. A different consideration must be made for foreign pregnant women which, in any case, constituted about 10% of the sample. This is also in relation to the large number of foreigners present in our territory, among which are many irregular pregnant migrants who landed on our coasts in recent years (Visalli *et al.*, 2020). In this group, we observed a clearly higher positivity for HBV than for HCV (2.0% versus 0.7%, respectively). Moreover, there were increasing trends for both HBV and HCV infection rates. Specifically, HBsAg detection ranged between 1.2% in 2016 and 2.4% in 2019 with a peak of 2.8% in 2017. For HCV, the positivity rate rose from 0.0% in 2016 to 1.2% in 2019. These findings suggest that especially HBV is still a problem in foreigners, probably due to lower vaccination coverage in this group of people.

## CONCLUSION

Our findings stress the importance of continuous surveillance of HBV and HCV markers in pregnancy and suggest that there is still much to be done to reduce the risk of these infections in pregnancy. Specifically, health education campaigns have to be carried out involving the general population and especially women in fertile age. These occasions should also spread the culture of prevention in terms of correct sexual behaviors and search for immune status against HBV, eventually advising HBV vaccination to women who test negative. Our previous studies highlighted the importance of health education regarding sexually transmitted infections, especially among students (Visalli *et al.*, 2014; Visalli *et al.*, 2019), and regarding vaccinations to fight the plague of vaccine hesitancy (Facciola *et al.*, 2019).

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## References

- Antonelli A., Ferri C., Fallahi P., Ferrari S.M., Ghinoi, A., et al. (2006). Thyroid disorders in chronic hepatitis C virus infection. *Thyroid*. **16**, 563-572.
- Bai H., Zhang L., Ma L., Dou X.G., Feng G.H., et al. (2007). Relationship of hepatitis B virus infection of placental barrier and hepatitis B virus intra-uterine transmission mechanism. *World Journal of Gastroenterology*. **13**, 3625-3630.
- Berkley E.M., Leslie K.K., Arora S., Qualls C., Dunkelberg J.C. (2008). Chronic hepatitis C in pregnancy. *Obstetrics and Gynecology*. **112** (2 Pt 1), 304-310.
- Bugianesi E., Salamone F., Negro F. (2012). The interaction of metabolic factors with HCV infection: Does it matter. *Journal of Hepatology*. **56**, 56-65.
- Calimeri S., Capua A., La Fauci V., Squeri R., Grillo O.C., et al. (2012). Prevalence of serum anti-rubella virus antibodies among pregnant women in southern Italy. *International Journal of Gynaecology and Obstetrics*. **116** (3), 211-213.
- Chen M.X., Fu X.D., Fan X.M. (2016). Perinatal hepatitis B infected parturients. Study on the correlation between the epidemic factors in umbilical cord blood and the epidemic status of newborns. *Journal of Hospital Infection*. **26** (24), 5686-5688.
- Connell L.E., Salihi H.M., Salemi J.L., August E.M., Weldeselasse H., et al. (2011). Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. *Liver International* **31** (8), 1163-1170.
- Di Pietro A., Visalli G., Antonuccio G.M., Facciola A. (2019). Today's vaccination policies in Italy: The National Plan for Vaccine Prevention 2017-2019 and the Law 119/2017 on the mandatory vaccinations. *Annali di Igiene*. **31** (2 Suppl. 1), 54-64.
- EASL. (2017). Clinical Practice Guidelines on the management of hepatitis B virus infection. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. *Journal of Hepatology*. **67** (2), 370-398.
- Elefsiniotis I.S., Papadakis M., Vlachos G., Vezali E., Tsoumakas K., et al. (2011). Presence of HBV-DNA in cord blood is associated with spontaneous preterm birth in pregnant women with HBsAg-negative chronic hepatitis B virus infection. *Intervirology*. **54**, 300-304.
- Epicentro. (2020). Bollettino SEIEVA-epidemiologia delle epatiti virali acute in Italia. Numero 6-aggiornamento 2019. Retrieved from <https://www.epicentro.iss.it/epatite/bollettino/Bollettino-6-marzo-2020.pdf>
- European Centre for Disease Prevention and Control. (2016). Epidemiological Assessment of Hepatitis B and C among Migrants in the EU/EEA. Retrieved from: <https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/epidemiological-assessment-hepatitis-B-and-C-among-migrants-EU-EEA.pdf>
- European Center for Disease Prevention and Control. (2020). Hepatitis B - Annual Epidemiological Report for 2018. Retrieved from <https://www.ecdc.europa.eu/en/publications-data/hepatitis-b-annual-epidemiological-report-2018>
- European Center for Disease Prevention and Control. (2020). Hepatitis C - Annual Epidemiological Report for 2018. Retrieved from <https://www.ecdc.europa.eu/en/publications-data/hepatitis-c-annual-epidemiological-report-2018>
- Facciola A., Visalli G., Orlando A., Bertuccio M.P., Spataro P., et al. (2019). Vaccine hesitancy: An overview on parents' opinions about vaccination and possible reasons of vaccine refusal. *Journal of Public Health Research*. **8** (1), 1436.
- Fensterl V., Chattopadhyay S., Sen G.C. (2015). No love lost between viruses and interferons. *Annual Review of Virology*. **2**, 549-572.
- Flores-Chávez A., Carrion J.A., Forns X., Ramos-Casals M. (2017). Extrahepatic manifestations associated with chronic Hepatitis C Virus infection. *Revista Española de Sanidad Penitenciaria*. **19**, 87-97.
- Gazzetta Ufficiale della Repubblica Italiana. (1991). LEGGE 27 maggio 1991, n. 165-Obbligatorietà della vaccinazione contro l'epatite virale B. Retrieved from <https://www.gazzettaufficiale.it/eli/id/1991/06/01/091G0201/sg#:~:text=La%20Camera%20dei%20deputati%20ed,nel%20primo%20anno%20di%20vita.>
- Gazzetta Ufficiale della Repubblica Italiana. (1991). CIRCOLARE 4 ottobre 1991, n. 20 Disposizioni relative all'applicazione della legge 27 maggio 1991, n. 165. Retrieved from <https://www.gazzettaufficiale.it/eli/id/1991/10/25/091A4650/sg>
- Guadagnino V, Stroffolini T, Caroleo B, Ippolito F.M., Rapicetta M., et al. (2013). Hepatitis C virus infection in an endemic area of Southern Italy 14 years later: evidence for a vanishing infection. *Digestive and Liver Disease*. **45**, 403-407.
- Hofstraat SHI, Falla AM, Duffell EF, Hahné SJM, Amato-Gauci AJ, et al. (2017). Current prevalence of chronic hepatitis B and C virus infection in the general population, blood donors and pregnant women in the EU/EEA: a systematic review. *Epidemiology and Infection*. **145** (14), 2873-2885.
- Hsu C.S., Liu C.H., Wang C.C., Tseng T.C., Liu C.J., et al. (2012). Impact of hepatitis B virus infection on metabolic profiles and modifying factors. *Journal of Viral Hepatitis*. **19**, e48-e57.
- Jinjuvadia R., Liangpunsakul S. (2014). Association between metabolic syndrome and its individual components with viral hepatitis B. *The American Journal of the Medical Sciences*. **347**, 23-27.
- Kumada T., Toyoda H., Kyriyama S., Sone Y., Tanikawa M., et al. (2010). Incidence of hepatocellular carcinoma in patients with chronic hepatitis B virus infection who have normal alanine aminotransferase values. *Journal of Medical Virology*. **82**, 539-545.
- La Fauci V., Facciola A., Riso R., Calimeri S., Lo Giudice D., et al. (2017). Seroprevalence of hev antibodies in a sample of pregnant women in the city of Messina. *Annali di Igiene*. **29** (3), 232-238.
- La Fauci V., Squeri R., Genovese C., Alessi V., Facciola A. (2020). The 'Dangerous Cocktail': an epidemiological survey on the attitude of a population of pregnant women towards some pregnancy risk factors. *Journal of Obstetrics and Gynaecology*. **40** (3), 330-335.
- Lao T.T., Sahota D.S., Suen S.S., Law L.W., Leung T.Y. (2012). Maternal HBsAg status and infant size--a Faustian bargain? *Journal of Viral Hepatology*. **19** (7), 519-524.
- Lao T.T., Sahota D.S., Cheng Y.K., Law L.W., Leung T.Y. (2013). Maternal hepatitis B surface antigen status and incidence of pre-eclampsia. *Journal of Viral Hepatology*. **20** (5), 343-349.
- Lao T.T., Chung M.K., Cheung T.K., Law L.W. (2016). Antenatal hepatitis B and increased risk of gestational diabetes mellitus - implications for obstetric care. *Journal of Infection*. **72** (5), 625-626.
- Leombo T., Saffioti F., Chiofalo B., Granese R., Filomia R., et al. (2017). Low prevalence of hepatitis B and hepatitis C virus serum markers in a cohort of pregnant women from Southern Italy. *Digestive and Liver Disease*. **49** (12), 1368-1372.
- Lo Giudice D., Capua A., La Fauci V., Squeri R., Grillo O.C., et al. (2014). Congenital rubella syndrome and immunity status of immigrant women living in southern Italy: a cross-sectional, seroepidemiological investigation. *Travel Medicine and Infectious Disease*. **12** (3), 253-257
- Ministero della Salute. (1998). Decreto Ministeriale 10 settembre 1998. Aggiornamento del decreto ministeriale 6 marzo 1995 concernente l'aggiornamento del decreto ministeriale 14 aprile 1984 recante protocolli di accesso agli esami di laboratorio e di diagnostica strumentale per le donne in stato di gravidanza ed a tutela della maternità. Retrieved from [https://www.gazzettaufficiale.it/atto/serie\\_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=1998-10-20&atto.codiceRedazionale=098A9129&elenco30giorni=false](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=1998-10-20&atto.codiceRedazionale=098A9129&elenco30giorni=false)
- Ministero della Salute. (2000). Circolare n. 19 del 30 novembre 2000. Protocollo per l'esecuzione della vaccinazione contro l'epatite virale B (D.M. 20 novembre 2000). Retrieved from [http://www.salute.gov.it/imgs/C\\_17\\_normativa\\_1517\\_allegato.pdf](http://www.salute.gov.it/imgs/C_17_normativa_1517_allegato.pdf)
- Morisco F., Loperto I., Stroffolini T., Lombardo F.L., Cossiga V., et al. (2017). Prevalence and risk factors of HCV infection in a metropolitan area in southern Italy: tail of a cohort infected in past decades. *Journal of Medical Virology*. **89**, 291-297.
- Ortega-Prieto A., Dorner M. (2017). Immune Evasion Strategies during Chronic Hepatitis B and C Virus Infection. *Vaccines*. **5**, 24.
- Pergam S.A., Wang C.C., Gardella C.M., Sandison T.G., Phipps W.T., et al. (2008). Pregnancy complications associated with hepatitis C: data from a 2003-2005 Washington state birth cohort. *American Journal of Obstetrics and Gynecology*. **199** (1), 38, e1-e9.
- Piconese S., Cammarata I., Barnaba V. (2018). Viral hepatitis, in-

- flammation, and cancer: A lesson for autoimmunity. *Journal of Autoimmunity*. **95**, 58-68.
- Reddick K.L., Jhaveri R., Gandhi M., James A.H., Swamy G.K. (2011). Pregnancy outcomes associated with viral hepatitis. *Journal of Viral Hepatology*. **18** (7), e394-398.
- Safir A., Levy A., Sikuler E., Sheiner E. (2010). Maternal hepatitis B virus or hepatitis C virus carrier status as independent risk factor for adverse perinatal outcome. *Liver International*. **30**, 765-770.
- Singh A.E., Plitt S.S., Osiowy C., Surynicz K., Kouadjo E., et al. (2011). Factors associated with vaccine failure and vertical transmission of hepatitis B among a cohort of Canadian mothers and infants. *Journal of Viral Hepatitis*. **18** (7), 468-473.
- Sirilert S., Traisrisilp K., Sirivatanapa P., Tongsong T. (2014). Pregnancy outcomes among chronic carriers of hepatitis B virus. *International Journal of Gynaecology and Obstetrics*. **126** (2), 106-110.
- Spada E., Tosti M.E., Zuccaro O., Stroffolini T., Mele A. Collaborating Study Group. (2011). Evaluation of the compliance with the protocol for preventing perinatal hepatitis B infection in Italy. *Journal of Infection*. **62** (2), 165-171
- Spiegel E., Shoham-Vardi I., Sergienko R., Landau D., Sheiner E. (2018). The association between birth weight at term and long-term endocrine morbidity of the offspring. *The Journal of Maternal-Fetal & Neonatal Medicine*. **32**, 2657-2661.
- Supriya D.M., Andallu D.R., Sashikala D.R. (2017). Study of Hepatitis B Virus Infection in Pregnant women And Their Outcome. *IOSR Journal of Dental and Medical Sciences*. **16** (1), 48-57.
- Tang C.M., Yau T.O., Yu J. (2014). Management of chronic hepatitis B infection: current treatment guidelines, challenges, and new developments. *World Journal of Gastroenterology*. **20** (20), 6262-6278.
- Terrault N.A., Levy M.T., Cheung K.W., Jourdain G. (2021). Viral hepatitis and pregnancy. *Nature Reviews Gastroenterology & Hepatology*. **18** (2), 117-130.
- Tse K.Y., Ho L.F., Lao T. (2005). The impact of maternal HBsAg carrier status on pregnancy outcomes: a case-control study. *Journal of Hepatology*. **43** (5), 771-775.
- Visalli G., Picerno I., Vita G., Spataro P., Bertuccio M.P. (2014). Knowledge of sexually transmitted infections among younger subjects of the city of Messina (Sicily). *Journal of Preventive Medicine and Hygiene*. **55** (1), 17-22.
- Visalli G., Cosenza B., Mazzù F., Bertuccio M.P., Spataro P., et al. (2019). Knowledge of sexually transmitted infections and risky behaviours: a survey among high school and university students. *Journal of Preventive Medicine and Hygiene*. **60** (2), E84-E92.
- Visalli G., Facciola A., Carnuccio S.M., Cristiano P., D'Andrea G., et al. (2020). Health conditions of migrants landed in north-eastern Sicily and perception of health risks of the resident population. *Public Health*. **185**, 394-399.
- Wang Y.Y., Lin S.Y., Sheu W.H., Liu P.H., Tung K.C. (2010). Obesity and diabetic hyperglycemia were associated with serum alanine aminotransferase activity in patients with hepatitis B infection. *Metabolism*. **59**, 486-491.
- World Health Organization. (2017). HIV and hepatitis coinfections. Available online: <https://www.who.int/hiv/topics/hepatitis/en/#:~:text=It%20is%20estimated%20that%20HCV,of%20people%20living%20with%20HIV>
- World Health Organization. (2020a). Hepatitis B. Retrieved from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>
- World Health Organization. (2020b). Hepatitis C. Retrieved from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>
- World Health Organization. (2020c). Hepatitis: Preventing mother-to-child transmission of the hepatitis B virus. Retrieved from: <https://www.who.int/news-room/q-a-detail/hepatitis-preventing-mother-to-child-transmission-of-the-hepatitis-b-virus#:~:text=In%20addition%20to%20the%20series,receive%20tenofovir%20prophylaxis%3B%20the%20preventive>
- Yazigi A., De Pecoulas A.E., Vauloup-Fellous C., Grangeot-Keros L., Ayoubi J.M., et al. (2017). Fetal and neonatal abnormalities due to congenital rubella syndrome: a review of literature. *The Journal of Maternal-Fetal & Neonatal Medicine*. **30** (3), 274-278.
- Zhao Z.Q., Pang Q.M., Wei W. (2017). Pregnancy with hepatitis B virus infection and carriers Influences on the prognosis of delivery. *Hebei Medicine*. **39** (16), 2496-2498.
- Zhou H., Chen Y., Duan Z., Zhang H., Pan C. (2012). Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. *Journal of Viral Hepatitis*. **19** (2), e18-e25.