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Monitoring viral infections in pregnancy by birth certificate attendance. The experience of province of Trento – Italy

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ABSTRACT

Introduction. Pregnant women can be subject to various types of infection that can have an impact on both the pregnancy and foetal health. In order to identify these conditions and institute the necessary treatments in a timely manner, guidelines recommend administering a series of serological screening tests, the timing and procedures of which are widely accepted by the whole scientific community. This paper reports on the coverage of serological screening during pregnancy and the seroprevalence of a series of viral infections amongst pregnant women receiving healthcare in the province of Trento (north-eastern Italy) between 2015 and 2019.

Materials and Methods. The data on serological screening during pregnancy are recorded on the birth attendance certificate (CEDAP) by the midwives present at birth, using an electronic template, at all maternity facilities in the province of Trento. The Authors retrospectively analysed the annual birth attendance certificate databases for all pregnant women who received care in hospital maternity facilities between 01.01.2015 and 31.12.2019. For cases in which a positive result, results pending or seroconversion were recorded, the hospital information system (*Sistema Informativo Ospedaliero*, SIO) was consulted to acquire information on the result of the test, the whole series of serological tests and any treatments prescribed. Serological screening coverage and seroprevalence were calculated for Rubella Virus, Cytomegalovirus (CMV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV).

Results. A total of 20,660 pregnant women were analysed. Average cover for all of the serological tests during the period considered was 97.5%, and no differences were observed with regard to the age group, academic qualifications and nationality of the pregnant women, or with regard to the maternity facility. The average seroprevalence of CMV virus was 69.5/100 pregnant women tested, with a significant downward trend during the five-year period analysed; for HBV it was 0.76/100, for HCV it was 0.39/100, for HIV it was 0.15/100 and for Rubella virus it was 90.5/100. The seroprevalence values followed an upward trend with a decrease in the pregnant woman's academic qualifications and were higher among foreign nationals. The seroprevalence of HBV infection was higher amongst mothers originating from Eastern European countries, for HCV and CMV amongst women from Asian countries and for HIV amongst those of African origin.

Discussion. The coverage observed for serological screening shows extensive compliance with the indications provided by Italian guidelines for the monitoring of pregnancy and homogeneous management of antenatal care throughout the province. The seroprevalence values obtained are largely consistent with those of previous Italian studies. Foreign women, younger women and women with a low level of schooling warrant special attention, also with a view to possible interventions to promote healthy lifestyles and access to vaccination schemes.

INTRODUCTION

During pregnancy, women can contract a number of infectious diseases caused by bacteria, viruses, protozoa or fungi. The risk of acquiring an infectious disease during pregnancy can be associated with the personal characteristics of the pregnant women, their belonging to high-risk categories, or failure to comply with hygiene and dietary practices, resulting in a higher risk of exposure to the pathogens [1]. A lack of vaccination - for example vaccination against hepatitis B or rubella - during childhood or in any case before the pregnancy, represents another considerable risk factor for infection [2]. An infection during pregnancy does not necessarily result in the development of a clinically overt disease, but it can have repercussions on the evolution of the pregnancy and the mother's health; it can also cause an infection of the foetus through transplacental passage, contact with the birth canal or breastfeeding. The effects on the foetus are any case conditioned by the time during the pregnancy at which the infection is contracted, by the timely identification and implementation of an effective treatment, if indicated [1, 2]. Consequently, in many countries it is recommended to carry out specific serological screenings during pregnancy, in the face of a certain variability in the prevalence of infections. More specifically, the Italian guidelines on the monitoring of physiological pregnancies recommend, at different stages of the pregnancy, the administration of tests for toxoplasmosis, rubella, cytomegalovirus, HIV, hepatitis B, syphilis and hepatitis C [3]. With the exception of CMV, these tests are included in the essential levels of healthcare, and consequently the pregnant woman is not required to cover any co-payment. Numerous studies have reported that these serological screening tests have favourable cost-benefit ratios, regardless of the prevalence values observed for the individual infections [2]. In the province of Trento, the recording of antenatal serological screening data has long since been a routine practice. The data is recorded, for each woman, in her personal antenatal guide, which is updated at each antenatal check-up and, for all pregnant women, when the birth attendance certificate (CedAP) is drawn up. In Italy, the CedAP is the reference document for the monitoring of the pregnancy, birth and the health of the newborn. Its completion by the health professional attending the birth, generally the midwife, is required by law. The CedAP must be drawn up, and then registered in the specific database of each ma-

ternity units, no later than the tenth day of birth [4]. Wishing to contribute to a greater knowledge of the phenomenon this study reports on the coverage of serological screening for viral diseases for which antenatal serological screening is recommended, and the corresponding seroprevalence values. The study population consisted of all pregnant women who received childbirth assistance at the maternity facilities of the province of Trento between 2015 and 2019.

MATERIALS AND METHODS

Serological screening for rubella is performed through the Rubeo test, which is carried out during the first weeks of the pregnancy through the determination of specific IgG and IgM antibody determinations. In the presence of a state of immunity (specific IgG antibodies positive and specific IgM antibodies negative), the test is not repeated. In the presence of a state of susceptibility (IgG and IgM negative), the test is repeated every 4-6 weeks, until at least the 5th month [3, 5]. Screening for HBV is performed during the third trimester using an HBsAg assay, with a confirmation test in the case of a positive result, and HBsAg and anti-HBc antibody assays if positivity is confirmed [7]. This is followed by a viral load assay on a plasma sample [3, 6]. The screening for HCV infection is performed during the first trimester by means of an HCV antibody determination using the ELISA (Enzyme-linked immunosorbent assay) method and in the case of a positive result, it is confirmed with the Riba (Recombinant Immuno Blot Assay) test. If the confirmation test is positive, a plasma viral load test and viral genotype analysis are performed [3, 7]. Screening for CMV infection is performed, in at-risk women only (pregnant women with flu-like symptoms, mothers of preschool children and women who work with preschool children), in the first trimester with specific IgG and IgM determinations. If the first antenatal serological test indicates prior CMV infection, the serological test is not repeated [3, 8]. HIV screening is recommended in the first trimester, during the first antenatal visit, and in the third trimester, and it is based on HIV-1 and 2 antibody assays using the immunoenzymatic method [3, 9]. In the province of Trento, the results of the serological tests for the viral diseases considered are recorded in the CedAP database at each maternity facility. The specific criteria for recording the results of serological tests in the CedAP database are shown in **Table 1**. This study included all pregnant women receiving

childbirth care in the province's maternity facilities between 01.01.2015 and 21.12.2019. For each case recorded in the CedAP as positive (HBsAg, HIV, HCV) or as not immune (Rubeo test), or with seroconversion (Rubeo test, CMV), or with results pending, the hospital information system (SIO) was used to verify/ retrieve full data. The SIO is a kind of electronic repository from which it is possible, for clinical or medicolegal reasons or epidemiological analyses, to retrieve all the analytical data regarding the healthcare services provided to residents and non-residents by the provincial health service. The coverage of the individual serological screening programmes was calculated retroactively, for each year in the study period and regarding the following maternal characteristics: age group, academic qualification and nationality, and for each maternity facility. The seroprevalence of the infections was also calculated for each year in the study period and with regard to the following maternal characteristics: age group, academic qualification and nationality. The retrieval of the whole serological profile of the positive cases allowed their clinical classification. The significance of the time trends for coverage and the seroprevalence of the individual conditions was analysed with the Cochran-Armitage test and the significance of the differences between the sub-populations compared, for both coverage and seroprevalence was analysed using the chi-squared test. The coverage and seroprevalence values are indicated together with the corresponding 95% confidence intervals.

RESULTS

Between 2015 and 2019, 20,660 pregnant women received childbirth care at maternity facilities of the province of Trento. 6.2% of the mothers had a premature birth (< 37 weeks of gestation) and a late prematurity (gestation weeks 34-36) occurred in 4.6% of cases. The average age of the pregnant women rose from 32.3 years in 2015 to 32.5 years in 2019 and the percentage of those of foreign nationality decreased from 26.3% in 2015 to 25.0% in 2019. Considering the entire panel of serological tests evaluated the average coverage over the study period was 88.6% and decreased from 95.3% in 2015 to 68.0% in 2019. Excluding CMV infection, the screening of which has never been included in the essential levels of healthcare for all women, but only those at risk, the average coverage for all screening programmes across the study period was

Table 1. Registration criteria in the CEDAP of serological tests in pregnancy for infectious diseases..

Serological test	Registration criteria
RUBEO TEST	1 not performed
	2 not immune
	3 immune
	4 in progress
	5 seroconversion in pregnancy
HBSAG	1 not performed
	2 negative
	3 positive
	4 in progress
	5 vaccinated
HCV - HIV	1 not performed
	2 negative
	3 positive
	4 in progress
CMV	1 not performed
	2 negative
	3 pre-pregnancy infection
	4 reinfection/reactivation in pregnancy
	5 first infection in pregnancy

98.5% and decreased from 98.9% in 2015 to 96.7% in 2019. The overall average coverage over the entire study period and excluding CMV is 95.0% in late or moderate preterm pregnancies and 91.0% in the case of very or extremely premature birth. Considering the screening programmes separately, average coverage was 99.8% for the Rubeo Test, 99.6% for HBV and HIV and 98.8% for HCV. Always excluding CMV infection, the temporal trend of coverage of all the serological screening tests considered collectively and for the individual tests was stable and without significant variations from one year to the next (**Table 2**). No differences in coverage were observed in relation to age group, academic qualifications or nationality, or in relation to the maternity facility where the birth took place. Of the entire population of pregnant women studied, 12,864 were positive for pregestational CMV infection (an average of 2,572 per year), 157 were HBsAg positive (on average 31 per year), of whom 4 (2.5%) had a history of drug addiction; 80 were positive for HCV (an average of 16 per year), of whom 22 (27.5%) had a history of drug addiction; 30 were positive for HIV (an average of 6 per year), of whom 2 (6.6%) had a history of drug addiction; 18,625 were found to still have rubella virus antibodies, *i.e.* to be immune (due to prior illness or vaccination), whereas 1,993 did not have antibodies and were therefore susceptible. Over the whole study period, the average seroprevalence for CMV

infection was equal to 69.5/100 pregnant women tested (95% CI: 68.8-70.2), HBV seroprevalence (positive HBsAg test) was 0.76/100 (95% CI: 0.65-0.87), HCV seroprevalence was 0.39/100 (95% CI: 0.31-0.47), HIV seroprevalence was 0.15/100 (95% CI: 0.09-0.21), and seroprevalence for rubella was 90.5/100 (95% CI: 89.95-90.65). The seroprevalence for CMV infection was statistically significantly higher ($p < 0.01$) in the age group 30-34 years and in the age group < 25 years; the seroprevalence for HBV infection was statistically significantly higher ($p < 0.01$) in the age group 25-34 years, for HCV in the age group 40 years and over, and for HIV in the age group < 25 years, while the level of immunity to rubella virus increased with an increase in age and, conversely, the proportion of susceptible subjects increased with a decrease in age, with a statistically significant trend ($p < 0.01$) (Table 3).

Seroprevalence and, in the case of rubella, the proportion of susceptible subjects (at risk of infection), increased for all the conditions considered with a decrease in the level of academic qualification, with a trend that was, overall, statistically significant ($p < 0.001$) (Table 4). Overall, a statistically significant excess was observed in seroprevalence amongst foreign women compared to Italian women (Table 5). Seroprevalence for HBV infection was higher amongst women from Eastern European countries (3.72/100), with a statistically significant difference

($p < 0.001$), compared to the mean values of foreign women, that for HCV was higher amongst mothers from Asian countries, with a statistically significant difference ($p < 0.001$), compared to the average values of foreign women; and that for CMV infection was higher amongst mothers of Chinese origin compared to the mean values of foreign women ($p < 0.05$). HIV seroprevalence was higher amongst pregnant women of African origin (1.10/100), with a statistically significant difference, compared to the average values of foreign women ($p < 0.001$). Lastly, the proportion of cases susceptible to rubella was higher amongst pregnant women from non-European countries compared to the average values of all foreigners, although this difference was not statistically significant.

As regards CMV infection, there were 169 cases of seroconversion during pregnancy (an average of 34 per year), of which 51.5% were reactivations and 48.5% were first observed during pregnancy. In absolute terms, overall seroconversions regard 141 Italian women, for a seroconversion rate of 1.0/100 pregnant women tested, and 28 foreign women, for a seroconversion rate of 0.60/100. Amongst the seroconverted foreign women, no statistically significant differences were observed regarding the geographical area of origin. As far as the Rubeo test is concerned, 4 seroconversions were recorded during pregnancy (less than one case per year), all of them in foreign wom-

Table 2. Percentage coverage of serological screening tests in pregnancy for viral diseases by single year. Period 2015-2019.

Serological test	2015	2016	2017	2018	2019
CMV	96.2	97.5	95.7	86.2	70.8
HBV	99.5	99.6	99.6	99.7	99.6
HCV	99.5	99.6	99.6	99.5	96.0
HIV	99.6	99.4	99.6	99.9	99.5
Rubella	99.9	99.8	99.9	99.7	99.8

Table 3. Seroprevalence of infections per 100 pregnant women (95% CI) by age groups. Period 2015-2019.

Age groups	Type of infections				
	CMV	HBV	HCV	HIV	Rubella (not immune)
< 25 yrs	78.70 (76.48-80.92)	0.52 (0.17-0.86)	0.39 (0.08-0.70)	0.39 (0.08-0.70)	15.62 (13.81-17.41)
25-29 yrs	71.06 (69.69-72.43)	0.96 (0.71-1.21)	0.30 (0.15-0.45)	0.09 (0.003-0.17)	12.32 (11.37-13.25)
30-34 yrs	79.45 (78.38-80.52)	0.99 (0.76-1.22)	0.41 (0.26-0.56)	0.13 (0.04-0.21)	10.18 (9.40-10.95)
35-39 yrs	67.74 (66.43-69.05)	0.45 (0.29-0.65)	0.33 (0.15-0.45)	0.13 (0.03-0.23)	7.68 (6.96-8.39)
≥ 40 yrs	68.46 (66.32-70.60)	0.46 (0.16-0.76)	0.77 (0.28-1.16)	0.26 (0.04-0.48)	8.37 (7.14-9.58)

Table 4. Seroprevalence of infections per 100 pregnant women (95% CI) by educational level. Period 2015-2019.

Educational level	Type of infections				
	CMV	HBV	HCV	HIV	Rubella (not immune)
University degree	64.68 (63.59-65.77)	0.47 (0.32-0.62)	0.22 (0.11-0.31)	0.09 (0.03-0.14)	7.77 (7.16-8.36)
High school	69.92 (68.97-70.87)	0.76 (0.59-0.93)	0.32 (0.20-0.42)	0.09 (0.03-0.15)	10.05 (9.45-10.63)
Middle school or lower	84.20 (82.08-85.60)	1.62 (1.16-2.06)	1.14 (0.76-1.52)	0.516 (0.25-0.77)	13.67 (12.42-14.90)

Table 5. Seroprevalence of infections per 100 pregnant women (95% CI) by citizenship. Period 2015-2019.

Citizenship	Type of infections				
	CMV	HBV	HCV	HIV	Rubella (not immune)
Italians	61.90 (61.1-62.7)	0.13 (0.08-0.18)	0.32 (0.23-0.41)	0.07 (0.03-0.10)	8.68 (8.24-9.12)
Foreigners	92.3 (91.5-93.0)	2.58 (1.83-3.33)	0.60 (0.40-0.80)	0.39 (0.23-0.55)	12.43 (11.55-13.31)

en from non-European countries. As regards clinical status, there were 3 certified cases of high viremia (> 10,000 copies/mL) amongst the cases of positive HBsAg tests (1.9%) and their overall classification is provided in **Table 6**. The acute forms prevailed amongst foreign women, the inactive forms amongst Italian women. There were 31 cases with high viremia amongst the HCV-positive cases (38.7%) and 6 cases with high viremia amongst the HIV-positive cases (20%). Amongst the 30 HIV-positive cases, the first confirmed positivity occurred during pregnancy in 5 cases (16%), all of them in women of African origin. There were three cases of HIV/HCV co-positivity, two cases of HIV/VDRL-RPR-TPHA co-positivity and two cases of HBsAg/HCV co-positivity.

DISCUSSION

The CedAP model used in the province of Trento provides for the acquisition of a much greater number of variables than that envisaged by in the “ministerial”

model. In particular, through our provincial model, all the serological tests proposed by Italian guidelines for the monitoring of physiological pregnancies are systematically acquired [3]. An overall analysis albeit preliminary, of the temporal trend of prenatal serological screenings in the province of Trento was carried out in a previous study [10]. In this study, an attempt was made to investigate the subject in depth in order to enhance the contribution of the staff of the maternity units. In fact, it must be said that the number of the variables to be acquired through the CedAP has been expanded, also including data on serological screenings, due to the willingness of health workers to monitor different aspects of the maternity care path. This information increase, together with the confluence of the annual electronic birth attendance certificate data at the Clinical and Evaluational Epidemiology Service of Trento Provincial Health Authority allows an analysis of all pregnant women who receive care in the province’s maternity facilities and, therefore, an area-based rather than a centre-based analysis. This also makes it possible to verify the level of application of recommended procedures for pregnancy care and the existence of any barriers to access to prenatal screenings. As regards the implementation of the recommended serological tests, it can be said that Italian guidelines appear to be fully applied at local level. The coverage values actually appear to be very high, with a negligible percentage of pregnant women not screened and without any difference in terms of the age group, academic qualification and nationality of the mother, or between the individual maternity units. As expected, coverage appears lower in preterm pregnan-

Table 6. Clinical status of HBV infection in HBSAg positive cases. Comparison between Italians and foreigners. Period 2015-2019.

Clinical status of HBV infection	Italians	Foreigners	Total
Acute hepatitis	1	9	10
Chronic Hepatitis	0	10	10
Previous Infection	3	84	87
Chronic Carrier	7	24	31
Inactive Carrier	6	13	19
Total	17	140	157

cies. It can therefore be stated that in the province of Trento there are no barriers to access to recommended serological screening in pregnancy, confirming the equity and homogeneity in the management of antenatal care in the area. However, it cannot be said that the reported coverage values are the best in Italy, also because this data is not currently registered at national level and therefore there is no possibility of comparison between different areas of our country. In any case, the small percentage of pregnant women not tested, CMV screening aside, is an issue that deserves consideration with regard to the causes and reasons. There is some time to close the CedAP after childbirth so, in the event that some assessment has not been made during pregnancy, it may be possible to do so, if appropriate, after childbirth. As regards the calculation of the seroprevalences of the various infectious diseases, a correspondence equal to 96% was observed between the data recorded in the CedAP and the data of the SIO regarding the positive cases. The quality of the data recorded in the birth attendance certificate can be considered satisfactory, although it was also necessary to access other information sources and not only to retrieve the results of the tests in progress, for which the results were not available before the birth attendance certificate was signed off. Use of other sources, such as the hospital information system was in any case necessary to retrieve all the data needed to define disease status, its potential for transmission to the foetus and any treatments instituted. The average proportion of women susceptible to rubella across the whole study period was 9.7%, which is substantially in line with the values reported by previous Italian [11] and international studies [12-14]. The percentage of women susceptible to rubella increased over time and was higher amongst younger women, those with a lower level of schooling and foreign women. This situation can be associated with a decrease in vaccination coverage over the past decade and with an increase in anti-vax movements, both aspects that should be considered when reviewing the vaccination programme offered to pregnant women and women of child-bearing potential [15]. HBV seroprevalence across the entire caseload of pregnant women coincides with that of a low-endemic area [16] and is similar to that reported in a previous Italian multicentre study [17]. There appears to be a very great difference in seroprevalence between Italian and foreign women that is higher than that reported previously in Italy [17], although it is consistent with more recent Italian studies [18, 19]. These differences can be in part

attributed to the different vaccination policies for the general public developed in previous decades in the different countries and will hopefully decrease in the future with the optimisation of vaccination programmes in the most endemic countries. HCV seroprevalence in pregnancy appears broadly stable over the study period and lower than that reported in the USA and most European countries [20, 21], and it is lower than the values reported in previous Italian observational studies [22-24]. Seroprevalence was higher amongst foreign nationals than amongst Italian women, in contrast with the results of previous Italian studies [23, 24], with an excess amongst those of Asian origin. The level of prevalence, in the province of Trento, is supported not only by foreign women from certain geographical areas, but also by mothers, many of whom Italian, belonging to certain risk categories. The most noteworthy of these is the presence of subjects with a history of drug addiction [25], which constitute 27.5% of HCV-positive mothers. Average CMV seroprevalence over the study period is within the range reported by previous Italian studies [26-28] and confirms that the values are higher amongst foreign women [27, 28] and also amongst those with a lower level of schooling. It would be useful, for reducing the risk of infection, to optimize prenatal or, better still, preconception counselling, aimed at promoting correct hygiene and dietary practices during pregnancy [29]. The overall prevalence of HIV infection observed is similar to that recorded in previous Italian studies [27, 30] and confirms that the value is higher amongst foreign women from African countries, where the prevalence of the infection amongst the general population is higher. The value reported in this study is also similar to that reported in the United Kingdom [31, 32].

CONCLUSIONS

In our experience, the CedAP has proved to be a very useful tool for monitoring the trend and characteristics of the infections, especially for viral infections during pregnancy. The inclusion of serological test results in the structure of CedAP allows to evaluate the adherence to the guidelines, the equity of access to serological screening and to calculate the prevalence of the infections in specific subpopulations of pregnant women. Lastly, combining data from the birth attendance certificate with hospital information system data makes it possible to classify the disease status and ac-

quire the information needed to analyse the management and the outcome of the treatment of the positive cases. As the birth attendance certificate includes a “neonate” section, it is also possible to analyse the neonatal outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

S.P., R.P.: Conceptualized the study. R.P., M.P.: Checked and corrected the data of the CedAP informative flow. R.P.: analysed the data. S.P., R.P.: Drafted the initial manuscript. S.P., R.P., M.P., L.D.: Interpreted the results and reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Study registration

N/A.

Disclosure of interests

All authors declare they have no conflicts of interest and they have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

Ethical approval

The Ethical approval was not required as this observational study involved fully anonymized data. The data come from the CedAP informative flow and are routinely collected according to the Italian laws in force. This study is in line with the STROBE and RECORD Statements.

Informed consent

Informed consent was not collected for reasons of organizational impossibility attributable to the fact that the failure to consider the data referring to the estimated number of interested parties who cannot be contacted to inform them, compared to the total number of subjects intended to be involved in the

research, would produce significant consequences for the study in terms of altering the relative results; this having regard, in particular, to the inclusion criteria provided for by the study, the methods of enrollment, the statistical number of the chosen sample, as well as the period of time elapsed from the moment in which the data relating to the interested parties were originally collected (as allowed by privacy code Legislative Decree 196/2003, by the provision of the Privacy Guarantor n.85 of 1 March 2012 and the provision of the Privacy Guarantor n.146 of 5 June 2019).

Data sharing

Data are available under reasonable request to the corresponding author.

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