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Viruses and genetics in pregnancy and birth

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ABSTRACT

In this study we presented several patients with genital infections during pregnancy, perinatal infection, de novo genetics syndromes, sterility problems and spontaneous abortions with HSV1, HSV2, CMV, Adeno, Parvo B19, RSV, EBV and Coxsackie virus. Spontaneous abortion were provoked (or at least associated) with viral infection. For some we had expected such pregnancy outcomes, and for some we observed chromosome breaks that by repetitive screening, after cessation of acute viral infection, could no longer been seen. Nonspecific chromosomal aberrations were associated with HSV type 2, herpes zoster and Ebstein Barr virus infection.

EBV is a causative agent of autoimmune entities were polyclonality in serological findings is present, we are searching for the same answer in the cause of spontaneous abortion with or without chromosomes abnormalities with atypical serology values of those viruses at both partners.

Keywords: chromosome breakage, viruses, perinatal infections, spontaneous abortions

INTRODUCTION

In the era of viral epidemics and pandemics, viral infection before, during and related to pregnancy become an important research thema. Pregnant women are particulary susceptible to some viruses, so serological testing for TORCH has long been in use.

During regnancy virus-infected women suffer worse outcomes (such as preterm labor and adverse fetal outcomes) than non-pregnant women and general population. New knowledges about the ways of interaction between maternal-fetal interface and placenta with the maternal immune system may explain these findings. Namely, during pregnancy woman's immunological system undergoes transformation in such a way to support pregnancy and growing fetus. When this protection is breached, as in a viral infection, this security is weakened and infection with other microorganisms can then propagate and lead to outcomes, such as preterm labor, spontaneous abortion and congenital viral syndromes (1,2).

Some viruses cross the utero-fetal barrier and some do not. Human viruses such as rubella virus, varicella-zoster virus, parvovirus B19, human cytomegalovirus (CMV), Zika virus (ZIKV), hepatitis E virus type 1 and HSV1 and 2, that replicate in the placenta, infect the fetus, and cause birth defects (3).

During pregnancy inflamation is regulated by cytokines (Th1 and Th2). In the begining of pregnancy first Th2, than Th1 predominate late in gestation. But when is abnormal may initiate the intensive cascade of inflamatory cytokine products involved in adverse pregnancy outcomes.

In addition to viral caused fetal infection, spontaneous abortion are caused also by hypoxia and innate immune response (4,5).

Epstein Barrvirus (EBV) is found in a aproximately 95% of the world’s population. It can be detected in the nasopharynx, blood, lymphoreticular tissue, for which it has a particular

affinity. The disease is transmitted from person to person by droplets. EBV may remain in the oropharyngeal epithelium and be excreted in saliva for a long time, perhaps for life, after infection, whether latent or manifest (6). EBV is involved in immune evasion and suppression of apoptosis that result in loss of tolerance and develompent of autoimmunity (rheumatod arthritis, multiple sclerosis, Reiter's syndrome) (7). Antigen mimicry is in the basis of EBV-linked autoimmune disese (8).

Viruses can produce at least three types of chromosomal changes: single breaks, pulverization of chromosomes, cell fusions and spindle abnormalities. Viruses induce chromosome breaks randomly and non-specifically. Some viruses that behave this way are: adenovirus, HSV types 1 and 2, herpes zoster, EBV, human CMV, hepatitis B, mumps, measles, rubella, poliovirus, and papilloma virus (9). For instance, HSV 1 and 2 induces chromosomal breakes by decondencing centromeric heterochromatin especially at chromosomes 1, 9 and 16. For acting this way HSV synthesize *de novo* early viral proteins responsible for induction of chromosomal damages. Specifically, it has been noted that that for double chromosome 1 defect (at locuses 1q21 and 1q42) host cells must be in a S-phase of cell cycle. In contrast to HSV, HCMV induces chromosomal breaks simply by entering the host cell and *de novo* viral protein expression. HHV6 integrates at telomere of chromosomes 17 and 22 (17p13.3 and 22q13.3). Finally, EBV nuclear antigen 1 (EBNA-1) induce double chromosomal breaks (10-12).

The incidence of spontaneous abortions is 12-15% in different population and 25-60% are with chromosomal abnormalities. In some families, pregnancy loss occurs more than once.

In addition to virus induced chromosomal damages, genetic factors, such as homozygotization of recessive mutations (runs of homozigosity, ROH) might also be associated with reccurrent pregnancy loss development (13).

During our 30 years practice in Genetic Counseling Unit, we have been frequently found seropositivity for EBV (EA or IgM) in couples who suffered recurrent miscarriages. Sometimes only in women, and sometimes in both partners. The phenomenon that viruses are significant in the occurrence of some changes related to pregnancy, childbirth and the newborn is found in many cases. The discovery that viruses in chronic infection or latent or polyclonality status are the cause of some cancer and autoimmune diseases inspire us to see whether recurrent miscarriages could be caused, at least in part, by viral infections.

1. CASE REPORTS

1. Herpes simplex virus 2 infection in pregnancy

The first pregnancy of a 30-year-old female who had a genital herpes in the early stage of her pregnancy ended by medically indicated abortion in 23rd week of pregnancy because of multiple fetal malformations. Given the patient's fear of the uncertainty of future pregnancies detailed advising encouraged the pregnancies that followed after 3 and 5 years. The pregnancies were closely monitored clinically and serologically. Considering the HSV IgM + and prodromal symptoms at the end of the second pregnancy and bearing in mind the child's best interest it was decided to end the pregnancy by Caesarean section. Healthy child was born. Between second and third pregnancy mother was HSV seronegative. However, during the course of third pregnancy mother developed clinically manifested herpes infection of the genital area three times. The decision was made to complete this pregnancy by Caesarean section to prevent vertical transmission of genital herpes. Pregnancy resulted in a birth of a healthy child.

The decision for Caesarean section is in accordance with guidelines recommended for women who have prodromal symptoms with genital herpes in history. Pregnant women with a history of recurrent genital herpes should be administered antiviral prophylaxis from 37th week of pregnancy.

2. CMV perinatal infection

Due to the slow clinical development during first 20 days after birth male infant was inspected by neuro pediatrician. At the same time his infection with CMV was confirmed. Later, at baby’s age of one-year, repeated control by neuro pediatrician revealed some speech problems as well as signs of rapid growth. The diagnosis of macrosomia was established. However, as metabolic, chromosomal, neurological as well as endocrinological cause were excluded, macrosomia was classified in favor of constitutional high growth (parents are tall).

The mother said that the boy reacts violently to stronger noises and high pitched voices, so we advised the examination at ORL clinic. She also confirmed his slower speech development and lessening in concentration. These symptoms are in clear accordance with intrauterine infection with CMV.

3. Coxsackie perinatal infection and encephalopathy

Male infant was born at Knin Hospital (BW/BL 3500gr/49 cm). Neonatal period has passed without any serious diseases. When 40 days old, the baby began to cough, and large fontanelle protrusion appeared. On the day of admission at Šibenik hospital a large fontanella bulge was even more noticeable and acute hydrocephalus was suspected. After lumbar puncture (pleocytosis: 1,352 gr /l protein, Pandy +) CT with contrast was made and suspected venous circulation disturbance in the rectus sinus area was confirmed. On the admission at Split Clinical Hospital, he was conscious, euphoric, normally hydrated, lively with spontaneous motility, BW 4170 g, HC 39 cm, fontanella 3×3 above surrounding bones, T. rec 37.8. In neurological status the musculature was slightly variable in tone, at traction the head occasionally went into opistotonus, tendon reflexes were brisk and patellar to the clonus. Lumbar puncture was performed again, and the liquor was under pressure, Pandy test was slightly opalescent (proteins: 0,44g/l cells: L 2/3), CSF culture was sterile. Urine culture was Enterococcus positive. Urinary ultrasound showed slightly wider duct systems on both sides. Fundus, ECG, EEG, MRI (no signs of circulatory disorder in rectus sinus area) all tested normal. The brain ultrasound was normal except that the cerebellum was imbued with fine-grained changes and enhanced echogenicity with radial drawing in white matter. The chest radiograph showed right suprahilar and paracardial consolidation of the lung parenchyma in terms of infiltration; 10 days after right bronchial pneumonic infiltrate paramedial supraclaviculary residuals were found. Discharged after 14 days of residency during which he received antibiotic parenterally and anti-edematous therapy. As there was no need for neurosurgical intervention we considered that it was an acute pneumonia with a consecutive transient increase in intracranial pressure and perhaps transient venous obstruction of the sinus rectus. After a couple of days, he was again hospitalized for a fontanelle bulge. Now lumbar puncture was performed again and cytological and biochemical analysis of CSF, CSF culture and CSF analysis by BK PCR and cultures were normal. Lung RT, ultrasond examination of the brain, EEG, PPD, hemo culture, ORL examination were performed and all parameters were within normal limits. For 11 days he was subfebrile and the fontanelle was slightly protruded in two occasions. Serology findings on perinatal viral infections have given us an etiological diagnosis. From the serum taken on the 5th day we received positive IgM and IgG titers of Coxsackie virus. All other causative agents gave only IgG + antibody titers, which were transmitted from the mother (CMV, EBV, Rubella, Mycoplasma pneumoniae, Adenovirus, HSV 1), while the titers for RSV, HSV 2 were negative.

Thus, we concluded that pneumonia and earlier upper respiratory tract infection were caused by the Coxsackie virus and that the clinical picture was dominated by CNS irritation with increased intracranial pressure and pleocytosis. We received no information on the epidemic of Coxsackie infections from Knin and Šibenik epidemiological services during the period May-June 1998, when Coxsackie virus infections occur.

Repeated serology testings showed a gradual decrease in the IgM and an increase in IgG antibodies. The boy's neurological development is monitored. He was treated for sideropenia for a long time and he had occasional upper respiratory tract infections with recurrence of a bulging of anterior fontanella. Increased IgG titers for Coxsackie were found in maternal serum. At the age of 18 months, all blood parameters, RTG and neurological status were within the age range.

4. Two cases of *de novo* chromosomal aberrations and translocations in two young men with sterility problems

First case. Sterility of the married couple (3 IVF and 2 inseminations) was indication for karyotyping. Short culture of peripheral blood lymphocyte with standard GTG banding was done for both spouses. Two consecutive chromosome analysis for the male patient showed aberration in 3 metaphases as follows: centromeric breakage of chromosome 8, complete deletion of short arm of chromosome 9, del(9p), centromeric breakage of chromosome 1 and long arm deletion of chromosome 9, del(9q31) with translocation between chromosomes 5 and 11, t(5;11) (Fig. 1-3). However, two months later repeated karyotyping showed normal male karyotype (46,XY) in all analyzed cells. Subsequently we were informed that during first two analyses the patient suffered from acute herpes zoster virus infection with clinical manifestation in the part of gluteal region. His wife had normal karyotype 46,XX,21ps+,22ps+ with a normal population chromosomal variants.

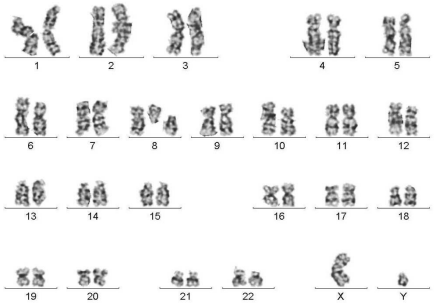

Figure 1. Centromeric breakage of chromosome 8.

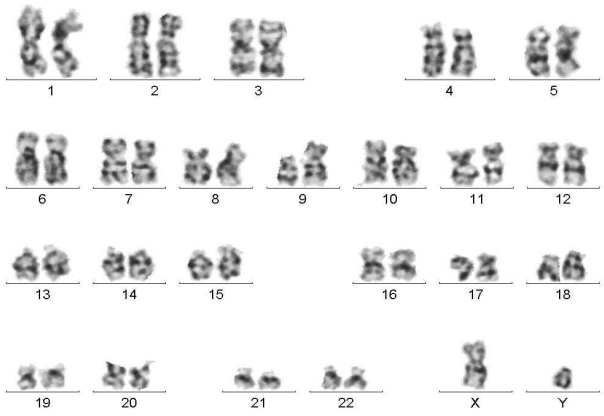

Figure 2. Long arm deletion of chromosome 9del (9q31)

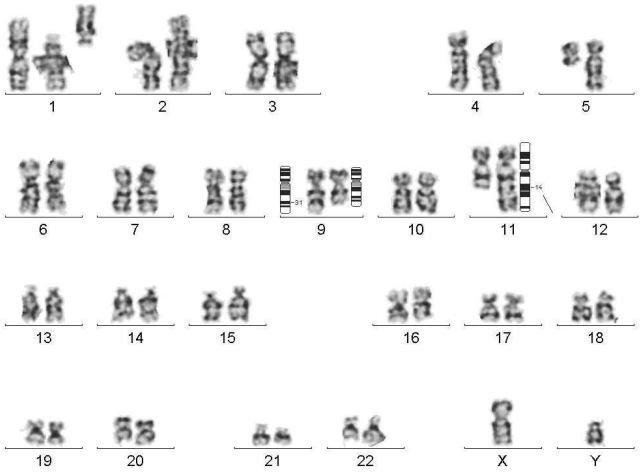

Figure 3. Centromeric breakage of chromosome 1 and long arm deletion of chromosome 9del (9q31) with translocation between chromosomes 5 and 1, t(5;11).

Second case. After the process of repeated unsuccessful assisted reproduction (IVF) due to the male azoospermia, and subsequent spontaneous abortion, couple attended the Genetic counseling unit. Both parents as well as aborted material were karyotyped. Trisomy 16 (47,XY,+16) was found in aborted material. Mother's karyotipe was 46,XX,21ps+,22ps+, and father's 46,XY(28)/46,XYY(2). At the same time, male viral serology showed EBV positivity (IgM, IgG, EA>150, EBNA 231,0). Virus was not confirmed by PCR. Husband's karyogram was repeated after three months. Standard karyotyping (on 30 cells) revealed only 2 cells with double Y chromosome (Figures 4 A, B and C).

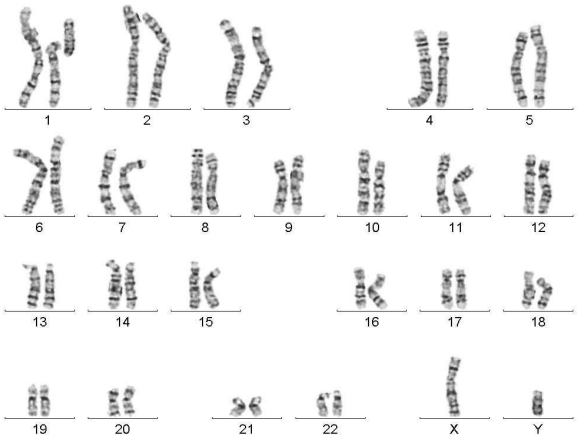

Figure 4. A) Breakage of the chromosome 1p.

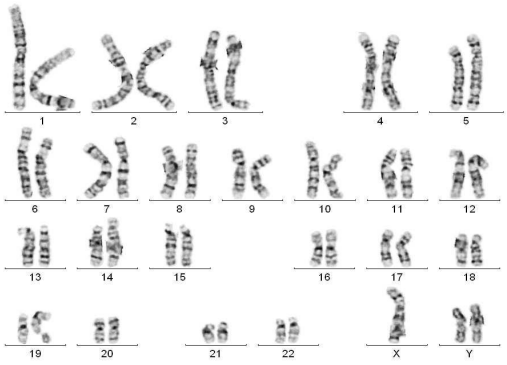

Figure 4. B) Breakage of the q arme of the chromosome 19 and double Y chromosomes.

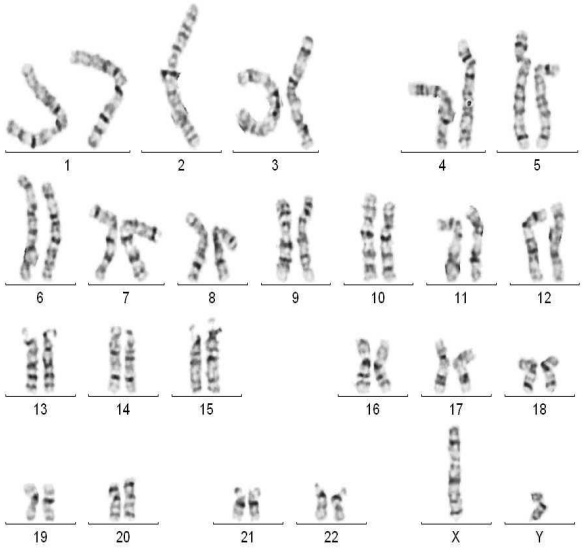

Figure 4. C) Breakage of Y chromosome.

5. *De novo* Noonan syndrome with transient leukocytosis and mother's EBV IgM positivity

The newborn female from the second regular pregnancy and normal birth 3 days after the date (BW 3900 g, BL 49 cm, AS 9) was admitted to Children's Hospital because of facial dysmorphism (eyes gently sloping, left blepharophimosis, wide root nose, flattened philtrum of nose, ear lobes protruding outward and above). She also had increased amount of skin on the neck, fetal hydrops, perinatal infection with heart defect (HD - atrial septal defect, ASD type II), infundibuliforme chest, hypotonia, hyperbilirubinemia and significant leukocytosis (78,000 leukocytes). Bone marrow biopsy showed the normal findings twice, and white blood cells counts over a two-month period had a tendency to fall. Changes in chromosomes by standard karyotype, FISH and MLPA were not found. Clinical suspicion for 3 possible syndromes was set: Noonan PTPN11, blepharophimosis-ptosis-epicanthus (*Foxl2* genes) and microdeletion 3q23. After next generation sequencing (NGS, at Yokohama City University, Japan) we found that the change occurred *de novo* in the *PTPN11* (exon 3:c.182A>G:pD61G) gene indicating Noonan (Figure 5) syndrome (mother's, father's and sister's NGS for *PTPN11* were negative), so we were able to give the genetic counseling. However, during that process we found that mother was positive for EBV IgM and was also positive after 5 years.

6. Spontaneous abortions and viruses

We retrospectively analysed documentation of 1.364 (2.728 persons) couples who attended Genetic counselling unit from 1987-2020. Of them 359 women and 289 men had positive viral serology findings for EBV (IgM, IgG, EA (early antigen), EBNA) (Table 1.).

Table 1. Number of individuals (both gender) with high titers of EBV (IgM, EA, IgG and EBNA) seropositivity

	Women	**Men**
IgM+, EA+, IgG>170, EBNA+ or >200	102 (51%) 199 100%)	49 (33%) 146 (100%)
IgG>170 only	60 (30.3%) 199 (100%)	41 (28%) 146 (100%)
EBNA >200 only	37 (18.7%)	56 (39%)

	199 (100%)	146 (100%)
Total number of individuals with very high positive titers Total number of individuals with positive titers	199 (55.6%) 359(100%)	146 (50.5%) 289 (100%)

Table 2. Number of individuals with IgM and IgG seropositivity for HSV1 and HSV2

Women			**Men**	
	IgM	IgG	IgM	IgG
HSV1	64 (16%)	336 (84%)	18 (5%)	275 (95%)
HSV2	9 (5%)	169 (95%)	6 (4.4%)	174 (96.6)

Table 3. Number of individuals with IgM and IgA seropositivity for Adeno and RSV

Women			**Men**		
	IgM	IgA		IgM	IgA
Adeno (N=22)	3 (13.6%)	1 (4.5%)	Adeno (N=21)	1 (4.8%)	0
RSV (N=12)	2 (16.7%)	1 (8%)	RSV (N=9)	0	2 (22%)

For other viruses we show percentage of IgM antibody only (Tables 1 and 2). However, IgM antibodies which indicates viral reactivation, was positive in considerable number of patients. The results for Adeno and RSV serology are presented in Table 3. The percentages of IgM nd IgA are higher than expected probably due to the infections witch happend during early pregnancies.

EBV reactivation or polyclonality was confirmed by positive IgM VCA and/or IgG VCA and/or EA IgG antibody, with positive EBNA IgG antibody. Couples were serologicaly analysed in a period from three months up to two years after they have had spontaneous abortion.

Paraffin embedded samples of aborted material of couples with positive serological findings were additionaly analysed for the presence of EBV by real-time PCR. Only ten samples were positive and could not confirm the placental EBV infection as a direct cause of the abortions. Average age of EBV serologically positive females/males was 33/36 years.

Chromosome analysis from peripheral blood showed normal karyotypes in 90% of samples; 10% of them have constitutional chromosomal variation. Most frequently the abortion

occurred in either 8th or 10th week of gestation. Both males and females had twice as higher history of number of spontaneus abortions among the siblings of second generation in relation to average population.

6.1. Couple with 4 spontaneous abortions with *de novo* microduplications

We are presenting a couple with one healthy child and 4 spontaneous abortions (at 7 weeks of gestation, 6 weeks, 10 weeks and at 21 weeks of gestation). In family pedigree data there were informations about siblings with spontaneous abortions on both sides. In patohystological anlisis of those 4 spontanoeus abortions there were signs of infections (chorioamnionitis and inflammatory infiltrates of granulocytes and lymphocytes some with calcifications).

Both parents have normal karyotypes. However, aCGH analysis performed at Institute of Medical Genetics, Tomsk National Research Medical Center, Russia, revealed husband's 14q22.1 microduplication 166.4 kb in size as well as 22q13.1 microdeletion 56.5 kb in size: arr[hg19] 14q22.1(51057729-51224090)×3, 22q13.1(39329035-39385485)×1. The maternal molecular karyotype was balanced.

Material from spontaneous abortion from the second pregnancy(6 weeks of gestation) was also analysed by aCGH. Fetus did't have the chromosomal rearrangements that father had. But *de novo* rearrangements in 11p11.2 and 11q13.1 regions with 323.8 kb and 240 kb in size were detected by aCGH: arr[hg19] 11p11.2(44282436446062 75)×3,11q13.1(65171314_65412205)×1.

Material from spontaneous abortion from the third 10 weeks of gestation) analyzed by aCGH also did not have chromosomal rearrangements that father had. However, it had duplication at 16q21 region with 7.1 Mb in size: arr[hg19] 16q21(59289759_66426705)×3, which were not seen in parents. Thus, the microduplication 16q21 in the fetus occurred *de novo*.

Spontaneous abortion from the fourth 21 weeks of gestation) had no unbalanced chromosomal changes according to aCGH results. Mother had EBV IgG 700, EA >150 and EBNA 494 in 2018. Than, again, in 2020 EA was >150 and EBNA 294. PCR from mother's blood for EBV was negative and explanation for this high serological results during 2 years was polyclonality or reactivation.

It is still debated whether EBV is a causative agent of autoimmune entities. We are searching for the same answer in the cause of spontaneous abortions with or without chromosomal or subchromosomal changings, depending of the time of viral reactivation and the time of conception.

DISCUSSION

Viruses can create various disadvantages in the human body. They can change genes expression, reduce host immunologial activity, provoke autoimmune reaction in the presence of some other infections (bacterial) but also in the presence of some other comorbidities significant for pregnancy (maternal sideropenia, for example). There is a lot of literature data on changes caused by viruses at the chromosomal level, such as chromosome breaks, chromosomal instability due to the action on the dividing spindle, but mostly described for cancer cells.

When talking about idiopathic spontaneous abortion, we believe that there is not a single mechanism for every gene or chromosomal change in embryo. Rather it depends on the time that passed between conception to abortion or the birth of a sick child, i.e. there is a mechanism that encourages this. The result is is a multifactorial disease - recurrent pregnancy loss.

In this study we presented several patients where abortion was provoked (or at least associated) vith viral infection. For some we had expected such pregnancy outcomes (CMV, HSV2, Coxackie), and for some we observed chromosome breaks that by repetitive screening, after cessation of acute viral infection, could no longer been seen (14).

ToRCH (toxoplasmosis, rubella, CMV, HSV) are the most common causes of congenital infections. Primary infections during pregnancy have wide ranges of clinical symptoms dependent on the stage of pregnancy. During the early stages of pregnancy infection causes congenital malformations, intrauterine growth restriction (IUGR) or fetal death. Infections during the later stages of pregnancy may result in latent (asymptomatic) babies at birth, which may progress to signs of infection at a later stage. The incidence rate of congenital toxoplasmosis is 1.5 cases per 1000 livebirths (15). Rubella virus is a major cause of birth defects and fetal death following infection in pregnant women (congenital rubella syndrome - CRS). About 0,5% of infants is born with congenital CMV infection. Some of them will have, and some will not, health problems later in life. Neonatal HSV infection incidence varies from 0.3 to 0.05 permille.

Cytogenetic analysis of Burkitt's lymphoma EBV positive and negative cells revealed a significant increase in dicentric chromosomes, chromosome fragments, chromatid gaps and increase of telomere size and telomere fusion in EBV-positive cells (16).

The damages during teratogenesis result as combination of cellular damages, effects of mitotic inhibition, and mitochondria, cytoskeleton, apoptosis are involved as well as gene expression changes (17). Herpes simplex virus-1 (HSV-1) latency-associated transcript (LAT) results in initiation of virus-specific $CD8^+$ T cells in latently-infected trigeminal ganglia (18).

In a large study conducted on 1,716 women experiencing spontaneous miscarriage in the first trimester of pregnancy no speciment was found positive for parvoB19V or CMV DNA. Seven specimens were positive for HSV-1/2 DNA. Serological testing revealed 47.24% of patients positive for parvoB19 IgG, 39.66% for HSV IgG, 79.31% for CMV IgG, and 9.31% for parvoB19 IgM. The high rate of positivity for CMV IgG suggests that the majority of women with first-trimester spontaneous abortions are not primary infected (19). Congenital CMV infection from initially seronegative mothers occured in 18 (3.0%) of 604 newborns and in 29 (1.0%) of 2.857 newborns born to immune mothers. Acquired immunity resulted in a 69% reduction in the risk of congenital CMV infection in future pregnancies (20).

CMV was identified in the semen of patients who were positive for IgG antibodies to cytomegalovirus and not in female serum. Semen samples from 109 men seeking fertility evaluation, prior to IVF treatment and no statistically significant associations were observed between semen parameters and viral presence. Viral DNA was detected in 54% of semen samples: HSV1/2 in 32 samples, EBV in 49, CMV in 47, HHV6 in 9, HHV7 in 4 and VZV in none. PS gradient failed to remove CMV in 89.36%, HSV1/2 in 59.38% and EBV in 22.45% of samples, while HHV6 and 7 were completely removed. HSV1/2 and CMV seem to persist even following PS treatment, so oocyte could becom infected during insemination, by IVF or intracytoplasmic sperm injection, with unknown sequelae (21-23).

CMV infection is a risk factor for centromere aberration in peripheral blood lymphocytes (24,25).

Parvovirus B19 could trigger SLE or closely mimics this condition (26). A causal link between viral infections and autoimmunity has been studied for a long time and the role of some viruses in the induction or exacerbation of systemic lupus erythematosus (SLE) in genetically predisposed patients has been proved. The strength of the association between different viral agents and SLE is variable. Epstein-Barr virus (EBV), parvovirus B19 (B19V), and human endogenous retroviruses (HERVs) are involved in SLE pathogenesis, whereas other viruses such as Cytomegalovirus (CMV) probably play a less prominent role (26). Human parvovirus B19 (B19) infection during pregnancy can results in cell death via

apoptosis ending in foetal death (27). Parvovirus B19 induce humoral and cellular immune response by virus-specific CD8+T lymphocytes (28, 29).

A study of the endometrium of women with herpetic infection has shown that early miscarriages (under 12 weeks) occurs as activation of cytotoxic natural killer (NK) cells with CD16 + phenotype and a strong suppression level of CD56 + cells endometrial type, and late miscarriages (13-22 weeks of gestation) occurs as cell deficit, followed by reduction of all CD8 + cytotoxic lymphocytes, and of CD56 + and CD16 + NK cells (30,31).

HHV-6, like other human herpesviruses, persists indefinitely in its host and is capable of reactivation. HHV-6 infection has the capacity to stimulate the effectors of innate immunity: an increased secretion of proinflammatory cytokines, such as interleukin-1(IL-1), TNF, and alpha interferon (IFN), while NK cell activity associated with IL-15 synthesis is elevated in HHV-6A infection (32).

Genomic instability of EBV-infected cells and defective immune surveillance system against such cells plays a critical role in determining the clinical manifestation of EBV infection. EBV infects B lymphocytes leading to their immortalisation, with persistence of the EBV genome as an episome. In the latent phase, EBV is prevented from reactivating through efficient cytotoxic cellular immunity. EBV reactivates (lytic phase) under conditions of psychological stress with consequent weakening of cellular immunity, and EBV reactivation has been shown to occur in a subset of individuals with each of a variety of cancers, autoimmune diseases, the autoimmune-like disease, chronic fatigue syndrome/myalgic encephalitis. Chronic EBV reactivation is an important mechanism in the pathogenesis of many such diseases (33-35).

Epstein-Barr virus infection is predominantly latent; however, lytic infection is detected in healthy seropositive individuals and becomes more prominent in certain pathological conditions (36,37).

Re-stimulation of T lymphocytes results in telomere damage that eventually leads to growth arrest or replication arrest, which then leads to activation of factors that initiate rest in memory T cells between episodes of viral reactivation responsible for long-term maintenance of T cell memory (EBV and CMV). Antibody production can take a lifetime. Human B lymphocytes proliferate into plasma cells in response to polyclonality which then allows serological memory to be maintained for life. EBV reactivation is closely related to cell cycle arrest in the Go / G1 phase (38-40).

Studies from Turkey found values with atypical serological findings for EBV in individuals with autoimmune diseases. The establishment and maintenance of Epstein-Barr Virus latent infection requires distinct viral gene expression programs, chromatin structure, and epigenetic modifications and chromatin remodeling (41-43).

Genetic instability is important in cancer as well as in cells affected by virus. Tumors show complex patterns of translocations, amplifications and deletions. In carcinomas with a genetic defect termed chromosomal instability; gains and losses of entire chromosomes, as well as segmental defects caused by chromosome breaks. The identification of centromeric breaks alongside aneuploidy in cells with spindle defects indicates that a single mechanism could account for all genetic alterations characteristic of chromosomal instability (44-46).

In female reproductive cells, there is a high number of numerical chromosomal changes (aneuploidy), which increase with age. Proper chromosome separation requires one or more crossovers within the DNA between homologous maternal and paternal chromosomes in combination with the coupling of the arms of the chromatid sisters. However, 25% remain in this state and this is called the maternal age effect (47). Embryonic aneuploidy occurs when chromosome aberrations are present in gametes or early embryos (48, 49).

Placental oxidative stress, with necrosis and apoptosis of trophoblastic epithelium and placenta, takes place in a low oxygen (O2) environment. In abortion, the development of the placental-decidual membrane is severely impaired due to maternal blood flow and large oxidative degeneration (50). The existence of the placental microbiota explains the colonization of the fetus / placenta by both pathogenic and commensal microbes (51, 52).

Presence of an entire additional chromosome, or chromosome loss, can affect the global genome methylation level.These results point out a possible link between aberrant epigenetic processes and etiology of mitotic non-disjunction (53,54).

CONCLUSION

Oncogenic viruses like adenovirus, herpes simplex type 1 and type 2, herpes zoster, EBV, HCMV, hepatitis B, mumps, rubella, poliovirus and papilloma virus, have been found to cause non-random, site-specific chromosomal damages. Those cases show nonspecific aberration in herpes virus type 2, herpes zoster and Esptein Barr virus infection in patients with genital infections during pregnancy, perinatal infection, *de novo* genetics syndromes, sterility

problems and SA. The theory of “two hits” for one unstable cell cycle resulting with aneuploidy is still in the basis of SA. EBV is a causative agent of autoimmune entities, such as MS, characterized by serological polyclonality. Does it act in the same way in development of SA with or without chromosomes abnormalities, indeed, depending on the time of viral reactivation, other coinfections and the time of conception?

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