of an activating KIR to its ligand [70]. Altogether, this highlights the importance of the balance between the activating and inhibitory signals in the activity of NK cells. Several studies have suggested that KIR genes may be also associated with the risk for other viral infections, such as hepatitis C, herpes simplex, BK polyomavirus (BKPyV), Epstein–Barr virus (EBV) and varicella zoster virus (VZV) [81].

8. KIR/HLA Interaction in Pregnancy Complication

Habitual miscarriages remain a problem for many couples. It is estimated that live births account for only 20–25% of fertilizations [82]. These occur more often due to women deciding to become mothers at a later age, complications of natural pregnancy or after in vitro fertilization. At least some of these problems seem to be a disorder of immune regulation. Uterine NK infiltrate the uterine mucosa and persist during normal pregnancy until delivery. It shows the importance of these cells not only for the implantation but also for the maintenance of pregnancy [83]. Uterine NK cells are close to the trophoblast cells and are therefore a determinant of maternal acceptance of the fetus. Uterine NK cells reduce cytotoxicity, which promotes the vascular formation of the arteries and enables trophoblast invasion by secretion of various cytokines, such as macrophage colony stimulating factor (M-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). They are necessary for the creation of an environment conducive to embryo implantation. Moreover, it has been shown that the secretion of growth stimulating factors from NK cells is essential for fetal growth [84]. Apart from the cytokine secretion properties, the properties of cytotoxic alloreactivity are also important. There is an hypothesis that maternal NK cells that carry a cytotoxic load are present in the uterus, where they recognize paternal HLA-C antigens on the surface of the fetus and trigger fetal damage. The balance between the regulation and activation mechanisms is crucial for the proper development of pregnancy. Many studies are focused on the role of NK cells in the implantation failure. Particular attention is focused on the KIR/HLA matching but the results are inconclusive. There are reports on the correlation between KIR AA haplotype, KIR BB and implantation failure/maintenance of pregnancy [85]. A recent study compared KIR haplotypes and the HLA-C genotype in the transferred embryo and its impact on pregnancy success. There have been 668 mothers with a single embryo transferred examined. The study revealed that KIR2DS1, KIR3DS1 and KIR2DS5 haplotypes were more frequent in spontaneous abortions and patients with the KIR A haplotype showed a lower risk of pregnancy loss compared to carriers of the KIR B haplotype. However, among the group of patients with the KIR A haplotype, the risk of pregnancy loss was significantly influenced by the presence/absence of the C1 allele in the embryo. The combinations (KIR A/homozygous C2 and KIR B/homozygous C1) led to up to 51% greater risk of loss compared to other combinations [86]. Similarly, the study by Soheil Akbari showed a significant association of maternal KIR2DS1 in combination with paternal HLA-C2 as a risk factor of spontaneous abortion [87]. Alomar et al. recently performed a study in which KIR/HLA associations were studied in recurrent spontaneous abortions (RSA). Sixty-five healthy women with a history of RSA (three or more spontaneous abortions) and 65 healthy controls (with at least two healthy children) were analyzed. The frequencies of KIR2DS2 and KIR2DL5A were significantly lower among women with RSA compared to the group of healthy women. No association with maternal HLA-C genotypes was observed. The analysis of the KIR/HLA-C combination showed the protective effect of KIR2DS2 with the HLA-C1 ligand. There are also reports that the KIR genes of haplotype B may have an impact on pregnancy success [88]. The possible participation in the initiation of pregnancy has been linked with the presence of the KIR2DL4 receptor. However, it is not conclusive as positive and no-effect studies can be found in the literature [89,90]. A recent meta-analysis of data from articles from the databases like Web of Science, PubMed, Scopus, Google Scholar, etc. was published by Iranian scientists. They concluded that KIR3DL1 was significantly linked with the protection from RSA. On the other hand, KIR2DS2 and KIR2DS3 alleles presented significant risk factors for RSA. There was no uniform conclusion for KIR2DS1 [91].