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Chapter

Human Papilloma Virus Infections in Pregnant Women and Its Impact on Pregnancy Outcomes: Possible Mechanism of Self-Clearance

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Abstract

Young women are at the maximum risk of human papilloma virus (HPV) infection which are asymptomatic in a majority of cases and spontaneously get cleared. Women in the age between 20 and 35 years are more active sexually and especially in the developing nations, this age group forms a major cohort among the population of pregnant women. The changed hormonal *milieu* and immune response during pregnancy might favor presence or persistence of HPV infection, while at the same time natural clearance also takes place during pregnancy with an unknown mechanism. Various HPVs have been reported to be associated with preterm rupture of membranes (PROM), fetal growth restriction (FGR), preeclampsia, placental abnormalities and preterm delivery in several populations. The risk factors involved in the intrauterine environment affects fetal development and thus increase the development risk of specific diseases in adult life as per the hypothesis of the fetal origins of adult disease (FOAD). The structural and molecular changes in the feto-maternal interface support and protect the semiallogeneic fetus from immune-mediated or inflammatory injury. On the other hand, the trophoblast cells of placenta facilitate the replication of HPV and the affliction of placenta and the vaginal infection can directly be associated with pregnancy outcomes. So, to optimize better child health care and reproductive outcomes, HPV screening might help during pregnancy. It is therefore important to understand how the HPV is affecting the early pregnancy and immune cells within the feto-maternal interface are educated for self-clearance to fulfill their biological functions or prevalence to affect the pregnancy outcomes and how the persistence of HR-HPV infection overtime increases the development of cervical cancer risk.

Keywords: pregnancy, self clearance, feto-maternal cell trafficking, HPV vaccine, cervical cancer

1. Introduction

The most common sexually transmitted infectious conditions across the globe are human papilloma virus (HPV) infections which is responsible for the

development of cervical cancer. The infection of HPV does not always lead towards the neoplastic disease which suggests that the clearance or acquisition of HPV infections may depend on the interpersonal variations in the immune system as well as environmental or viral factors. For example, a well-established cervical cancer risk factor is parity. However, the influence of pregnancy in the natural history of HPV infection and thus the development of cervical neoplasia and its exact mechanism is not known [1].

At the beginning of the pregnancy, immune modulation and induction of tolerance are required for successful implantation allowance but as the pregnancy progresses a responsive immune system is responsible for a successful pregnancy which can protect both the fetus and the mother against environmental insults whenever there is a necessity arises. Indeed the maternal immune system reinforces networks that can respond according to the recognized danger signals and eliminate them appropriately promoting repair when needed. Not only the maternal immune system but also the actively developing immune system in the fetal-placental unit can modify further the maternal immune response and the reaction of the maternal immune system to the environment. So, the immunity during pregnancy is dynamic and unique which can be modulated as per the requirement and definitely not suppressed [2].

Several studies have proven the idea incorrect that constant immunosuppression is crucial for a successful pregnancy which demonstrates that inhibition of key signaling pathways such as pathways mediated by FAS; FAS ligand and deletion of immune cells at the implantation site are detrimental to pregnancy which may lead to pregnancy loss [3, 4]. The deletion of specific decidual NK cells leads to poor endometrial vascularity and obstruct the invasion of the trophoblast [5]. Thus, for a successful pregnancy the presence of immune infiltrates is required which suggests that the immune cells are not recruited to the decidua as a response to a 'non-self' or 'foreign' fetus but recruited actively to facilitate proper implantation and promote successful pregnancy.

During pregnancy and postpartum, different levels of hormonal changes and changes in the immunity may be responsible for the modulation of the natural history of the HPV infection. There are differences in the status of HPV infection during pregnancy and reduction in the number of HPV positive cases during postpartum period have been reported by various authors [6]. Though the dynamics of HPV infection during pregnancy is not well understood and the information remains controversial. The clearance and persistence of HPV during and after pregnancy have been studied by very few authors [7].

HPV infection in most cases naturally disappears in a short relative time period and risk of disease development in that case is very less. As pregnancy affects the host immune system, it is believed that pregnancy reduces the seroreactivity against infection of HPV. The upstream regulatory region of HPV18 has been reported to be activated by estrogen and progesterone which alters the clearance rate of HPV compared to non-pregnant women [8]. HPV genotypes and viral characteristics such as population distribution and evasive ability play an important role during persistent infection. However, how the HPV genotype specific reaction of the host immune system and the sexual behavior of pregnant women affect the rates of infection in case of persistent cases and how it is related to the host in not clear [9].

In pregnancy, the pregnant mother which is an adult organism is exposed to the fetus which is partly an extremely young organism and this phenomenon can be viewed similar to a natural state known as parabiosis in which organisms share partly blood systems. However, the fetus may have restoring effect on the maternal system. It has been reported that the regenerative capacity of the aged liver and other organs in mice model is restored by pregnancy [10].

There are controversial results on the risk of HPV infection in pregnant women. A higher HPV prevalence has been reported in few studies in pregnant women, whereas, some claimed there are no statistical difference among the age matched non-pregnant women [9]. Moreover, there are no studies on estimating the trimester, age and type specific prevalence of cervical HPV DNA in pregnant women.

This chapter will focus on the incidence of HPV infection in pregnant women population, the reason behind higher incidence rates in early pregnancy, the possible mechanisms responsible for self-clearance and non-clearance of HPV in pregnant women, immune mechanisms playing role in pregnancy, feto-maternal cell trafficking and how HPV affects the pregnancy outcomes. Furthermore, we will also discuss the potential of HPV infection during pregnancy can lead to the development of cervical cancer and therapeutic strategies.

2. Incidence of HPV infection in pregnant women population

Highest incidence rates have been reported in young adults just after the onset of their sexual activity [11]. In young women between the age group of 17 and 24 years, longitudinal studies reported incidence rates of HPV infection ranging from 15.7 to 29.4 of all types per 1000 women-months [12]. Women in their thirties showed a lower incidence rate in cohort studies which is between 5.2 and 13.4 any type HPV infection per 1000 women-months [12]. The prevalence is likewise higher in younger age groups than older. The global HPV prevalence estimated by a multi-country meta-analysis is 11.7% (with confidence interval 95% 11.6–11.7%) with normal cytology in women with an important variation within and between geographic regions. At round 25 years the prevalence peaks and decreases thereafter. It has been reported that at around 45 years a smaller second peak is observed [13, 14]. It has also been reported in various studies that within 1–2 years of HPV infection almost 80% of them resolve spontaneously [15]. Various studies suggested that during pregnancy it is more likely to acquire and progress HPV infection [16] which regresses after delivery [6, 7, 17, 18].

Whereas, Liu et al. [16] reported that in pregnant women the HPV prevalence varies from 9.58 to 46.67% and in age-matched non-pregnant women the prevalence varies from 8.9 to 23.5%, with a summary estimate of 16.82 and 12.25% respectively and there are significant differences between the summary estimates. In Asia, North America and Europe, it has been reported that the HPV prevalence rates are significantly higher in pregnant women as compared to those in non-pregnant women and the pregnant women in North America as compared to those in Europe and Asia are more susceptible to HPV infection [16]. As per the meta-analytical data showed by Liu et al. [16], the prevalence rates of HPV infection in pregnant women in North America, Australia, Europe and Asia were 30.37, 36.60, 13.19 and 15.72% respectively which showed a worldwide significant difference. In pregnant women aged 25, 25–29 and ≥ 30 years the prevalence rates of HPV infection were 23.94, 13.34 and 14.79% respectively and in non-pregnant women the prevalence rates were 18, 12.08 and 11.43% in respective three age groups [16]. The most frequently identified HPV types in pregnant women have been reported are HPV-16 with 3.86% prevalence rate, HPV-6 with 2.45% prevalence rate, HPV-18 with 1.80% prevalence rate and HPV-11 with 1.76% prevalence rate which is as same as the prevalence rates in non-pregnant women of these HPV types. In the three trimesters the HPV prevalence rates reported are 18.20, 14.38 and 19.32% and the odd ratios are 1.59, 1.20 and 1.71 respectively as compared to the non-pregnant women population.

Studies conducted in Hong Kong and Hungary showed that in asymptomatic pregnant women HPV-16 is the most common type and HPV-6,-18,-11,-58,-31 and – 33 are the other common HPV types [19]. Whereas, in non-pregnant women the sequence is bit different such as HPV-16, -6, -11, -18, -58, -33 and -31 and in women with normal cytology worldwide the sequence reported is HPV-16, -18, -31, -58 and -52 [16].

Specific to genital tract infections, HPV types are classified into three risk categories based on their relative malignant potential such as HPV-6, -11, -40, -42, -43, -44 are low risk; HPV-31, -33, -35, -51, -52 are intermediate and HPV-16, -18, -45, -56 are high risk types. Young women between the ages of 10 and 35 years are reported to be at the maximum risk of HPV infection which are asymptomatic in majority of the cases and spontaneously get cleared may be due to the strong immune system. The reason being this is the age when women are sexually more active. A major cohort of the pregnant population is formed by this age group in the developing nations. The changed immune response and hormonal *milieu* during pregnancy might favor the presence or persistence of the HPV infection. Niyibizi et al. [18] reported the prevalence of HPV infection in pregnant women with a wide variation from 5.5 to 65%. Various HPVs in several populations have been reported to be associated with adverse pregnancy outcomes such as preeclamsia, preterm rupture of membranes (PROM), preterm delivery, fetal growth restriction and placental abnormalities. However, no such data on the association of the HPV infection in pregnancy and its outcome from the Indian subcontinent is available till date [20].

3. The reason behind higher incidence rates in early pregnancy

3.1 Maternal immunity during pregnancy

Starting at the conception and towards the course of completion with labor and birth enormous transformations the uterus has to undergo in pregnancy. In order to achieve blastocyst stage embryo development for a newly fertilized egg and successful invasion into the uterine tissue, there is a requirement of finely balanced subsets of immune cells and their soluble mediators. Mainly genetics determine the developmental potential of the blastocyst. However, the optimal environment of the uterus determines the viability and competence of the blastocyst to become a fully developed fetus and on-time delivery achievements which in turn reflects the maternal immune response quality.

It has been claimed that pregnancy is a state of mild immunosuppression due to the reduction in the helper T-cell type 1 cell mediated response or decrease in natural killer cells. Sillman and Sedlis in the year 1987 reported that a higher incidence of cervical neoplasia is found in immunosuppressed women [15]. A steroidal hormone receptor binding element present on the transcriptional promotor of HPV-16 as reported by Gloss et al. is responsible for promotion of HPV transcription which suggests an involvement of hormonal activation of replication of HPV [21]. Observation from various studies indicated that the temporary altered immunity state and the increased steroidal hormonal levels during pregnancy might have an influence of the subsequence progression of the disease development effecting on HPV replication [16].

Fetus inherits 50% genome from the father that leads to the expressing of antigens which are acknowledged as foreign by the maternal immune system. To accommodate the semi-allogeneic fetus within the immunocompetent mother's body a range of complex processes take place [22]. The physiological and immunological

changes during pregnancy marks it a unique condition that makes the mother and the fetus more susceptible to certain infectious diseases, risk of congenital anomalies and the risk of more serious outcomes in other diseases. These changes are mainly driven by the cytokines, hormones and immune cells that lead to the modification of the immune system as well as the structural changes by remodeling of the endometrium [23]. In the 1950s, it was initially proposed that the induction of general immunosuppression during pregnancy allows the tolerance of the semi-allogeneic fetus and since then several hypotheses has been proposed explaining the reason why the fetus is not rejected by the maternal immune system (**Figure 1**).

On the contrary, after the natural infection pregnant women are capable of inducing immune responses and immune memory which is similar to non-pregnant women which proves the above hypothesis wrong [24]. Various studies have reported that the modulation of the immune system rather than active suppression is observed during pregnancy. Over the course of pregnancy, the progressive increase of the concentrations of steroidal hormones such as progesterone and estrogens induce a shift in the balance of pro and anti-inflammatory responses. During the first trimester of pregnancy which is called "open wound phase" the pro-inflammatory responses are prominent and in the second and the third trimester phases where the body prepared for deliver the anti-inflammatory responses are prominent [22]. Thus, it is clear that why the severity of certain diseases such as multiple sclerosis, rheumatoid arthritis induced by the inflammatory responses are often gets reduced during the third trimester of pregnancy and diseases which are controlled by the inflammatory responses such as malaria, influenza and lupus are increased during this phase [25]. There is a shift from Th1, which is oriented towards cell-mediated immunity, towards Th2, which is oriented towards the hormonal immunity, responses is observed which is associated with an alteration of the balance between type1 and type 2T helper cells and this transition is needed for the development of a healthy fetus. The suppression of cytotoxic T lymphocytes and stimulation of B lymphocytes to further increase the production of antibodies that are potential to be transferred to the fetus is controlled by these Th2-skewed responses. The findings of Mor et al. [22] and Chaouat et al. [24] suggested that the placenta is capable of interaction and response to pathogens which makes it an active immunological site. At the feto-maternal interphase, the immune mechanisms contribute to protect the fetus from rejection providing required cytokines and growth factors for implantation of the fetus in the

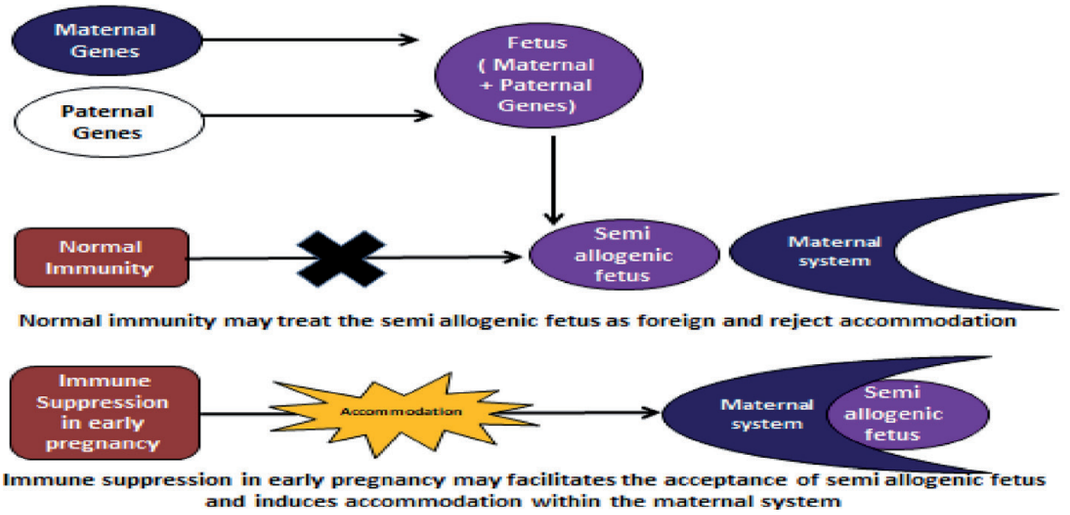

Figure 1.
Accommodation of the semi-allogenic fetus in the maternal system.

placenta. The placenta can generate signals which may modulate the responses of the maternal immune system to pathogens which leads to a new paradigm that there is a combination of signals and responses originating both from the feto-placental unit and the maternal immune system which decides the overall immunological responses during pregnancy (**Figure 2**) [26].

3.2 Anatomical changes during pregnancy

The increased susceptibility to infection of pregnant women during pregnancy may be due to the immunological and anatomical changes of the uterine canal. Like other human viruses, the placenta or the cells of the fetal origin may get infected by HPV. The presence of HPV has been reported in the polymorphonuclear cells which suggest that the passage of virus through feto-maternal barrier may be allowed by the transfer of the maternal cells [27]. It has also been reported that the trophoblast cells are broadly permissive *in vitro* for HPV and within the trophoblast cell cultures this virus is able to complete its life cycle [28, 29].

In the uterine mucosa, especially in the postovulatory phase there is an increase in the circulating progesterone levels which initiates a cascade of molecular and cellular events that allows the initial anchor of the embryo to the epithelial layer of the endometrial surface further leading to the coordination of the invasion of the extra-embryonic trophoblast lineages. The proliferative activity of estrogen-primed endometrium is inhibited by progesterone which induces the secretory activity in the glandular compartment followed by triggering the influx of specialized uterine natural killer cells such as uNK; CD16/CD56bright in response to the production of local chemokines such as CXCL9, CCL4 and CXCL10. The Uterine natural killer (uNK) cells which are a rich source of angiogenic and growth factors, has been reported to have critical role in remodeling of the endometrial spiral arteries during and prior to pregnancy [5, 30]. The contractile activity of the myocytes of the junctional zone is strongly reduced by the progesterone which is a crucial process for the apposition of the blastocyst to the luminal epithelium. The most outstanding aspect of the maternal response during pregnancy is the transformation of the endometrial stromal fibroblasts into epithelioid-like, secretory decidual cells.

Upon implantation of a blastocyst, decidualization of the stromal compartment is observed in most species. On the other hand, in humans decidualization is initiated without the involvement of a pregnancy in the midsecretory phase of the cycle. It is progressive process which is at first initiated around the terminal spiral arteries

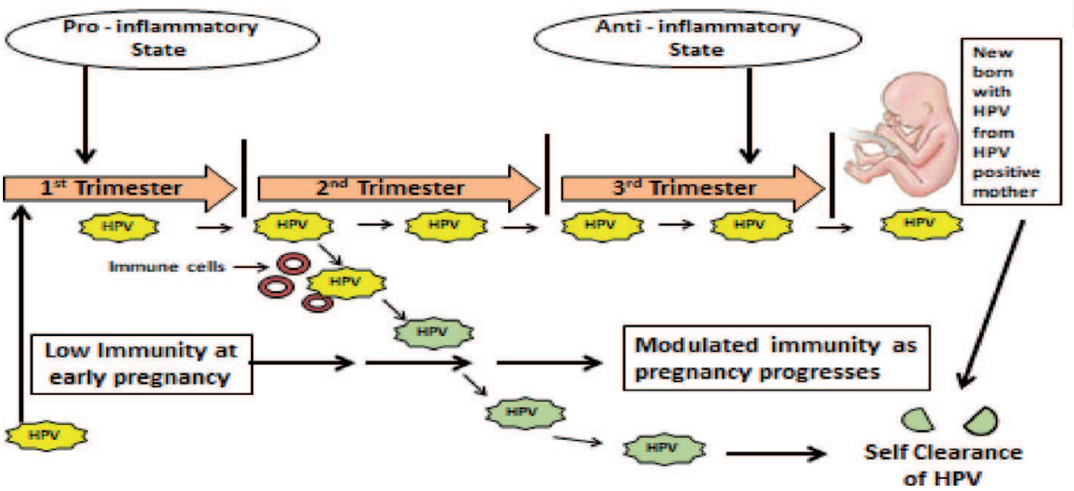

Figure 2.
HPV clearance and non-clearance during pregnancy and postpartum.

of the superficial endometrial layer which continues in pregnancy involving the entire endometrium as the pregnancy progresses [23]. The invasive or extravillous trophoblastic cells mediate the attachment of the placenta to the maternal uterine wall and they are responsible for the establishment of a low-resistance, high-flow supply of the maternal circulation to the fetus and the placenta. The placental dysfunction occurs due to the failed invasion of the extravillous trophoblast cells leading to the adverse obstetric outcomes such as spontaneous preterm delivery and pre-eclampsia. There are controversial reports on the HPV infection of the invasive trophoblast cells and their effects. There are reports showing the evidence of detection of HPV in trophoblast tissue from early pregnancy losses where HPV was more prominently found in spontaneous abortion cases than in cases of elective terminations of pregnancy. The genomes of the four different HPV types such as 11, 18, 16 and 31 are reported to undergo complete life cycle in 3A trophoblast cell lines and the HPV-31 in an in vitro system are shown to decrease cell number of the trophoblast cell and their adhesion [31].

Impaired placental function is associated with pregnancy loss or complications such as abruption, fetal growth restriction and pre-eclampsia. In this case we have to consider that the uterine remodeling during pregnancy is required to accommodate deep trophoblast invasion and the decidual process is not primary under the embryonic control which makes the implantation process more vulnerable to perturbations in the mother [23].

4. The possible mechanisms responsible for self-clearance and non-clearance of HPV in pregnant women

4.1 Role of maternal immunity

Between the maternal decidua and the blastocyst the first point of contact is represented by the trophoblast. It has been reported by current studies that the trophoblast plays an active role during implantation and early placentation in shaping the immunological milieu by educating and attracting immune cells at the implantation site and thus modeling the subsequent response of the immune cells to external stimuli. Cytokines such as transforming growth factor-β (TGF β), CXCL12 which is also known as SDF1, CXCL8 which is also known as IL-8 and CCL2 which is also known as MCP1 are constitutively secreted by trophoblast cells. The secretion of these cytokines by trophoblast cells upon establishment at the implantation site, promotes the recruitment of neutrophils, peripheral monocytes, T cells, NK cells and Treg cells [32]. After decidualization although immune infiltrates are already present, studies have shown that for successful pregnancy, immune cell trafficking is crucial and any disruption in these chemokines signaling pathways leads to reduced infiltration of the immune cells and adverse pregnancy outcomes. Cytokines are also secreted by trophoblast cells that can act on immune cells after their recruitment. These secreted cytokines have been reported to stimulate the unique differentiation of the earlier recruited immune cells in such as a way that they acquire phenotypes which are collectively essential for the successful pregnancy [33].

Decidual NK cells are less cytotoxic, thus they are different from peripheral NK cells and TGFβ12 and trophoblast-derived IL-15 induces this type of phenotypes. Decidual vascular remodeling which is crucial for development of the placenta targeted by these specialized NK cells [34]. CD14+ monocytes upon recruitment to the maternal-fetal interface acquire a unique phenotype that is M2-like macrophage which might be induced by the trophoblast-derived macrophage colony-stimulating

factor (M-CSF) and IL-10 [2118]. These M2-like macrophages participate in clearance of apoptotic cells and phagocytosis of degraded extracellular matrix and play a crucial role in tissue remodeling [35]. Trophoblast-educated M2 like macrophages on the contrary to other tissue-resident macrophages, maintain their CD14 expression and capable of immunomodulatory cytokine secretions such as type I interferons and TGFβ [35]. Trophoblast-derived TGFβ furthermore is able to induce the naive CD4+ cell differentiation into FOXP3+ Treg cells [36]. In addition to the trophoblast cells, a substantial amount of data have shown that the decidual cells also have vital role in regulation of the immune cell trafficking which is mostly T cells towards the site of implantation (**Figure 3**) [37, 38].

In addition to chemokines and cytokines secretion which attract and educate immune cells, numerous studies have shown that the trophoblast cells have the ability to sense and respond according to the microenvironment. Cell-surface receptors expressed by the trophoblast cells such as NOD-like receptors (NLRs) and TLRs can recognize specific molecular patterns within the microenvironment. These receptors have also the ability to recognize DAMPs which are basically released from damaged tissues and dying cells as well as PAMPs (Pathogen-associated molecular patterns) from viruses, bacteria and other microorganisms and thus permit the trophoblast cells to sense and response to these signals [39, 40]. Thus, the placental and fetal development is supported by the trophoblast cells attracting and educating immune cells and responding to the signals within the microenvironment in a unique way such as decidual differentiation followed by trophoblast migration and invasion, angiogenesis and finally spiral artery remodeling [41].

4.2 How pregnancy responses to viral infections

During pregnancy the consequences of viral infection can vary being a benign asymptomatic event which is undetected mostly and it can either cause the occurrence of fetal congenital malformations or pregnancy loss [42]. Like bacteria, the TLRs and NLRs expressed by the immune cells as well as those expressed by the trophoblast cells can be engaged by the viruses. Viral replication as well as vertical transmission of a virus to the developing fetus from the mother can also controlled by the trophoblast cells [43, 44]. Commensal bacteria which are present at the

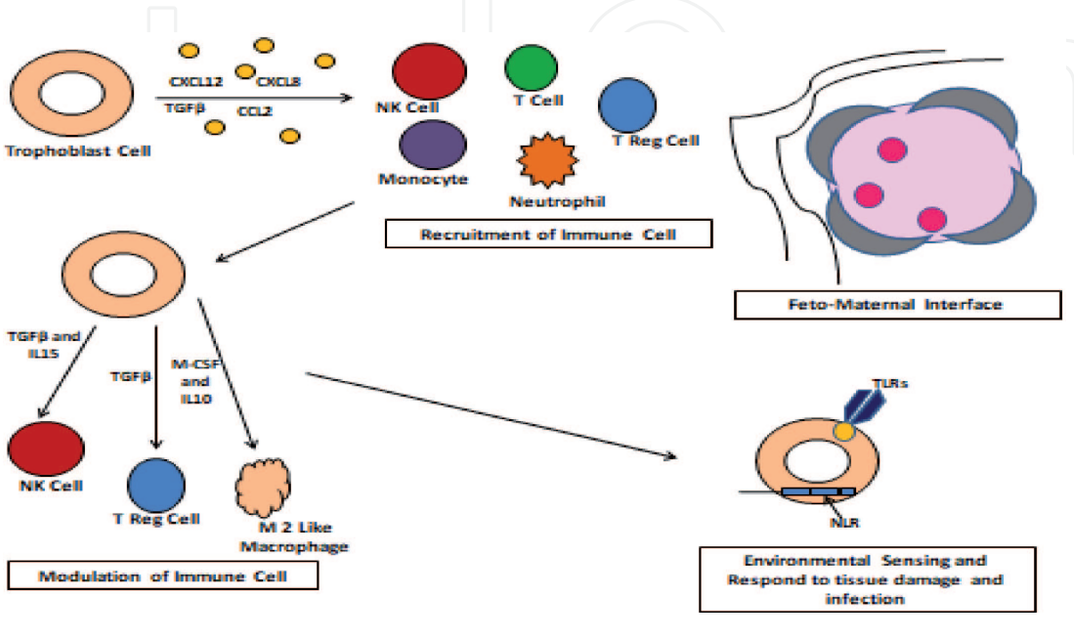

Figure 3.
Immune modulation during pregnancy at the feto-maternal interface.

feto-maternal interface can induce the secretion of IFNβ by trophoblast cells which supports the decidual receptivity by exerting immunomodulatory effects. It has been reported that the antiviral responses can be exerted by the IFNβ [45] and thus one of the molecular pathways that is type I IFN pathway is actively inhibited by the viruses as they establish as infection. Various studies in mouse model have demonstrated that by inhibiting IRF3 phosphorylating in the placenta, viral infection can decrease IFNβ expression which leads to the decreased antiviral responses [46]. TLR4 induced responses are modified by viral infections to commensal bacteria leading to the conversion of pro-inflammatory from anti-inflammatory in nature [47]. The receptivity and tolerance at the feto-maternal interface is promoted by the IFNβ which suggests that blunted response of IFNβ secondary to viral infection is responsible for the detrimental pregnancy consequences. The reduced receptivity of the immune cells at the feto-maternal interface due to the loss of IFNβ also reduces their capacity to control and respond to other microorganisms. Thus, the association of the overwhelming inflammation with pregnancy complications suggests that there may be an involvement of an undetected viral infection which can change the response pattern of the feto-maternal interface to commensal bacteria. This hypothesis has been supported by the study results of Cardenas et al. [48] using an animal model. In that study, pregnant C57BL/6 mice was infected with MHV68 on 8.5 embryonic day and a low dose of LPS subsequent administration on E15.5 day leads to a cytokine storm which was characterized by high levels of G-CSF, CXCL1, IL-8 and TNF which is associated with parturition, a reduced production of IFNβ followed by preterm birth. These changes in the cytokine profile leading to preterm birth is not induced alone either by LPS treatment or MHV68 infection but by a 'double-hit hypothesis' proposed by Mor et al. [41] which suggests that how trophoblast cells respond to bacterial products are changed by a viral infection which abolishes the normal microbiota immunomodulatory effects. In response of the commensal microbiota, the trophoblastic cells in the absence of a viral infection secret IFNβ, whereas IFNβ signaling is abolished in the presence of a viral infection leading to eradicate its immunomodulatory effects which in turn changes the response of the trophoblastic cells to commensal bacteria shifting IFNβ response to a cytokine storm which promotes preterm birth. However, it has been reported that the inflammation and preterm labour is also promoted either by an increased response of IFNβ or inhibition of the IFNβ regulators [49]. Thus, the original milieu which has a setting of immune-tolerance, during viral infection, is shifted into a state of pro-inflammatory condition [41].

4.3 Role of feto-maternal cell trafficking

During pregnancy there is a bidirectional cell passage exists between fetus and mother which is called feto-maternal cell trafficking. It is known as fetal microchimerism when there is a presence of fetal cells in the maternal circulation and maternal microchimerism when the maternal cells are present in the fetal circulation. Georg Schmorl in the year 1893 first reported about fetal microchimerism after identifying the placental trophoblast cells in a mother who died due to eclampsia [50]. The persistence of fetal cells in the maternal circulation [51, 52] and other maternal organs such as liver, heart, kidney [52] and bone marrow [53] has been reported decades after pregnancy. In 1963, with the identification of the maternal platelets and leukocytes in the cord blood the maternal microchimerism was described for the first time [54]. In healthy, immunocompetent individuals these maternal cells have been found to circulate into adult life [55].

At 7 weeks of pregnancy the bidirectional trafficking of the cells begins and increases throughout the gestation steadily and peaks at parturition [56]. In normal pregnancies, maternal microchimerism and fetal microchimerism has been

reported to be 42 and 51% respectively at the time of delivery [57]. In human blood and tissues the detection of maternal-fetal microchimerism is done by in situ hybridization for identification of whole cells and the identification of the origin of the DNA whether it is from mother or the fetus is done by polymerase chain reaction (PCR) to identify Y-chromosome DNA sequences in mother [58]. As the Y chromosome is easier to distinguish it is used as a biomarker to detect microchimerism and it does not require the fetus to be male. However, male microchimerism has been reported to be found in a fifth of women with no birth of a male child. The possible reason of the phenomenon can be a vanished male twin; early miscarriage of a male embryo; transfer of male cell through the maternal circulation from an older sibling to a later pregnancy; or due to an unexplored possibility of transfer of male DNA into the maternal circulation during sexual intercourse [59]. In females, male fetal cells have reported to show increased antigenicity. As the fetus carries paternal genes among which some are expressed on the cell surface that may induce potent allogeneic responses the mother confronts an immunological challenge during pregnancy. However, in spite of the immunologic differences of the cells, the fetus does not get rejected frequently (**Figure 4**) [60].

In pregnancy, the maternal and fetal cell exchange is common. During gestation, placenta allows the fetal and maternal reciprocal transport of cells in a state of mutual tolerance which proves placenta is not an immunologically inert barrier. It is not necessary to continue a pregnancy and deliver a child to develop mirochimerism. Up to 500,000 nucleated fetal cells can be delivered into the maternal circulation even early terminations from surgical abortion [61, 62]. The cellular movement across the placental barrier is controlled by the maternal, fetal, or/and placental signals rather than nonspecific leakiness. The involvements of integrin-dependent and VEGF pathways are associated with the trans-placental cell trafficking mechanism but the initiation of the processes by the exact molecular signals are yet unknown [63]. In case of preeclampsia, fetal surgery and pregnancy termination where there is a disruption of the feto-maternal interface, association of altered feto-maternal cell trafficking has been reported which suggests that the placenta has a role in the cell migration regulation. The altered microchimerism levels are also associated with histocompatibility differences which suggests that the cell trafficking and the survival of the trafficked cells is either promoted or hindered by the immune response between the fetus and the mother [64, 65]. During pregnancy, the biological role of the bidirectional movement of cells is unknown, although it has implications in the fetal immune system development [66]; repair of tissue in autoimmune disease [67–70] tolerance mechanisms during pregnancy [71]; immune surveillance

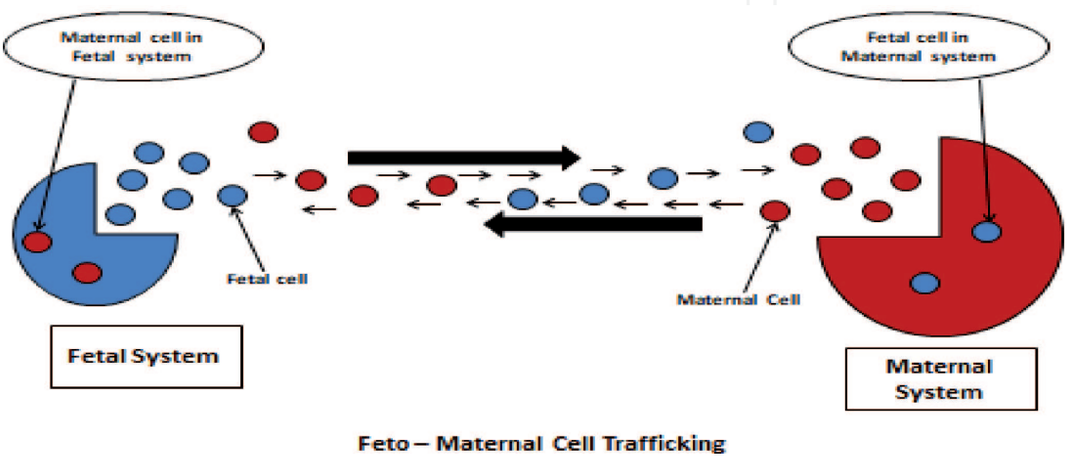

Figure 4.
Feto-maternal cell trafficking during pregnancy.

[72] and cancer [73]. It is also involved in the maintenance of balance between the tolerance [74] and immunologic priming [75] which can influence the occurrence of autoimmune disease and transplantation outcomes. The utility of the feto-maternal cell trafficking has been identified clinically in the prediction of pregnancy complications [76, 77] and in prenatal testing for aneuploidies [78].

The research on microchimerism is still in its infancy, more specifically on the fetomaternal microchimerism. In women with autoimmune diseases, the long-term existence of the fetal cells and its speculative role has not yet been studied well. It has been reported by some of the researchers that the microchimeric cell populations occur due to pregnancy may have stem cell like properties which have the potential to home in damaged tissues and organs and further differentiate as part of the maternal repair response [62].

5. How HPV affects the pregnancy outcomes

Merckx et al. [79] reported that children born to HPV-positive mothers are at a significantly higher risk of becoming HPV positive which further results in infantile genital and anal condyloma acuminatum and juvenile laryngeal papillomatosis. However, by the age of 6 months some HPV infections are almost cleared. Hence, the question regarding susceptibility of pregnant women to HPV infection and its prevalence as compared to non-pregnant women population are crucial to answer [16].

Various studies reported that spontaneous abortion occurs in up to 30% of all pregnancies and it constitutes one of the most frequently occurring adverse pregnancy outcomes worldwide. In 5–13% of deliveries, spontaneous preterm birth is also observed [80]. As per the reports of recent investigations, the human papillomavirus infection of the placenta may be involved with placental abnormalities, spontaneous preterm delivery and spontaneous abortion.

Trophoblast cells as discussed earlier constitute the prime target for HPV in placenta which is responsible for placentation abnormality. Various studies showed that in pregnant women the prevalence of HPV infection ranges widely from 6 to 65% and the HPV DNA has been detected in amniotic fluid, placenta, fetal membranes and umbilical cord blood [81].

Delivery before 37 weeks of gestation is defined as preterm birth and it is an important complication worldwide for both multifetal and singleton pregnancies. As compared to children born at term, the preterm children are more likely to develop log-term neurological and developmental disorders and are at an increased risk of mortality. The highest rates of preterm delivery have been reported to be found in South-eastern and South Asia with a percentage of 13.4%. Especially in low-income countries, the morbidity and mortality are highest among these preterm children [80].

As per the fetal origin of adult disease (FOAD) hypothesis, the specific changes in the fetus are caused by the intrauterine environmental exposures which lead to the risk of developing diseases in adult life. Depending on the environmental interaction, these risks may lead to adult diseases. Coronary heart disease was documented earlier to support this hypothesis [82] but a range of chronic conditions has also now been included to expand the framework [83]. While, the 'thrifty phenotype' hypothesis states that low birth weight babies should not be at high risk of non-insulin dependent diabetes development when they grow with a scarcity of food [84, 85] but growing up in an area of affluence of the same babies would increase the risk and hence the intrauterine exposure plays an important role in inheriting the harmful potential in interaction with exposures later. Thus, the

reformulated FOAD hypothesis included epigenetics and the life –course epidemiology as an important factor which includes social and physical exposures during gestation, adolescence, childhood, young adulthood and adult life. To understand the development of chronic diseases, history specific and inter-generational elements of individual's life is also important [86]. The timing of exposure variables and how the outcome of interest is related to each other is the basis of life-course perspective. Hence, the effects of intrauterine exposures can be modified by the entire lifespan of an individual through the life-events, behavioral, biological and socioeconomic processes [87].

Infection with HPV (Human papillomavirus) is generally regarded as sexually transmitted disease. However, the detection of HPV in the oral mucosa of newborn babies who are sexually inexperienced has been reported in various studies which suggests plausible non-sexual alternative route of HPV infection. Detection of HPV genotypes and their similarities in the offspring's oral sample and in mother's genital tract suggests that the probable source of HPV infection in the newborn is the HPV infected mother. In the mother-baby pair, the reported vertical transmission rates are between 18.2 and 53.3% [88].

The possible mode of vertical transmission of HPV to infant from a mother is still under debate. However, during fertilization, or pregnancy or delivery the possible mode of transmission has been implicated. Evidence of prenatal transmission of HPV has been provided by Koskimaa et al. [89] and the presence of HPV in cord blood and placenta has been shown to increase the risk of carrying HPV DNA in the oral mucosa which suggests that in the transmission of HPV, unlike several other human viruses, placenta may play an important role [27]. Recent studies reported that the placenta and the maternal microbiomes have role in regulating the neonatal microbiomes which suggests during pregnancy the fetal exposure of microbiota has long-term outcomes in their health [90]. The translocated maternal oral microbes are presented to the fetal immune system at the placenta which acts as a site leading to the development of prenatal tolerance to the maternal microbiome [91].

The encounter with HPV and its significance in pre or perinatal period is not clear. Early exposure of HPV might have a significant impact in the HPV-specific immunity development, subsequent HPV infection and progression due to the immaturity of the immune system of the fetus and infant [92]. However, practically in children the HPV-specific immunity has remained an unknown area. As reported by Koskimaa et al. [88] and Koskimaa et al. [93], children aged 12–14 years had immunoreactivity specific to HPV 16 E2-, E6-, and E7. Whereas, various studies reported that the HPV-16 specific cell mediated immunity is much lower in adults [94, 95]. Between HPV positive and negative subjects, differences have been found in the memory Th cell (T Helper) reactivity against HPV16 E2, E7 and E6 oncoproteins in adults. Against HPV16 E2 and E6, the Th responsiveness is accompanied by the type 1 and type 2 cytokine secretions in a mixed pattern and seems to be more common in healthy individuals as compared to individuals with HPV16 induced disease.

Koskimaa et al. [89] reported that children those are exposed to HPV via cord blood or Oral HPV or placenta might have HPV16 specific T helper cell responses similar to the adults having HPV induced lesions which are highly different from negative HPV controls.

Though some studies have reported HPV infection to be associated with spontaneous preterm delivery and spontaneous abortion, controversy continues in this field due to the reason that some studies were unable to confirm this association.

6. Potential of HPV infection during pregnancy can lead to the development of cervical cancer and therapeutic strategies

Cervical cancer ranks as the 3rd most frequently diagnosed cancer with an estimated 569,847 incident cases and 311,365 deaths reported in the year 2018 (GLOBOCAN) worldwide and in women it is the fourth leading cause of death due to cancer. After breast cancer it ranks second in incidence and mortality rates in lower HDI settings. Worldwide in 28 countries it is the mostly diagnosed cancer and leading cause of cancer death in 42 countries which includes vast majority in South-Eastern Asia and Sub-Saharan Africa [96]. It has been reported that around 530,000 women get affected every year by cervical cancer and the HPV related cancer burden in women worldwide add up to 6% of total cancer cases.

In India, the diagnosis of new cervical cancer is about 96,922 cases annually making it the 2nd leading cause of female cancer. Women aged between 15 and 44 years, cervical cancer is the second most common female cancer in India [97].

The development of cervical cancer and its precursor lesions are reported through several epidemiological and biological studies to be associated with high-risk human papilloma virus (HPV) infection. The development of high grade cervical lesions is reported to be associated with positive high-risk HPV test results in women with or without abnormal cervical smears [66, 98–100]. It has been reported in various studies on immunocompromised patients such as transplant recipients and AIDs patients that the increased persistence of high-risk HPV and HPV-mediated carcinogenesis is associated with compromised immunosurveillance [101, 102]. In pregnancy, the immune-response is altered in women and some studies concluded that there is no effect of pregnancy on CIN [103], whereas few reported high relapse rates of cervical dysplasia in the postpartum period [104]. Likewise, few studies reported high-risk HPV prevalence rate to be higher in pregnant women and others reported there is no difference of HPV prevalence between non-pregnant and pregnant women. However, on the natural course of high-risk HPV types infection the influence of pregnancy is not yet known. There are few questions need to be answered in this area: (1) what is the difference between the clearance of HPV in pregnant and non-pregnant women? (2) During pregnancy how does the high-risk HPV rate change? [6].

The Food and Drug Administration (FDA) has approved three vaccines such as the first-generation human papillomavirus (HPV) vaccines, Gardasil (Merck, Kenilworth, NJ, USA) which is a quadri valent vaccine; Cervarix (GlaxoSmithKline, London, UK) which is a bivalent vaccine, have the potential to prevent about 70 and 84% of the cervical cancer cases respectively. Gardasil 9 (Merck), which is a next-generation nonavalent HPV vaccine, can prevent cervical cancer approximately 90%. However, pre-existing infections and their related cervical abnormalities cannot be treated by these vaccines. The American Society of Clinical Oncology (ASCO) in the year 2016 released cervical screening guidelines which recommend the screening for women aged between 30 and 49 years, one to three times in a lifetime in lower resource settings [105]. The screening should be done with primary HPV testing via the use of self-collected specimens as it has been reported to be more effective, adaptable and reliable method of screening as compared to traditional cytological methods and thus the effective cervical cancer screening can be done in several generations of women [106].

In terms of HPV vaccination and coverage rates of cervical screening, considerable inconsistencies exist worldwide between countries and within countries. In low-income and middle-income countries (LMICs), in the year 2008 the reported overall screening uptake was 19%, while in high-income regions it was 63% [107].

As compared to high-income countries, in low-income and middle-income countries the HPV vaccination coverage is much lower. In the high-income countries an estimated 33.6% of girls and women aged between 10 and 20 years had received the full course of HPV vaccine by the year 2014 as compared to low-income and middle-income countries which was 2.7% of the same age group of females [108]. Though studies are still in progress on the long-term vaccine efficacies to understand the total duration of protection, it has been reported that with Gardasil the protection against targeted HPV types last for at least 10 years [109], with Cervarix at least 9 years [110] and with Gardasil 9 a least 6 years [111]. But these vaccines have not sufficiently been tested during pregnancy and hence it is not used in pregnant women.

The Centers for Disease Control and Prevention (CDC) recommends HPV vaccination for women having either an HPV infection or an abnormal Pap test or both if they are in the appropriate age group as that may protect them against the high-risk HPV types which have not been acquired by them. However, the vaccination has not the potential to treat the abnormal results of the Pap test or cure the current HPV infections [112]. Though, the vaccines have been reported to be safe when given to people with pre-existing HPV infection, it gives maximum benefit if given to people before being sexually active [113, 114]. However, some residual benefit from the vaccination will still be there for people already exposed to HPV even though infections with one or more HPV types which are included in the vaccines. Currently, there is no specific test available to detect past exposure of HPV in individuals and the approved HPV tests detect only current infection with high-risk HPV types at the cervix region without any information on past infection.

Even after the vaccination, the screening for cervical cancer need to be done as all HPV types which has the potential to cause cancer are not covered by the HPV vaccines. Therefore, in cervical cells to detect precancerous changes before the development of cancer, screening is essential. Additionally, women with existing HPV infection or who are not vaccinated the cervical screening is critically important. However, the screening recommendations may be changed in future for women given HPV vaccination.

Research works are in progress to develop therapeutic HPV vaccines which would prevent cancer development among women with previous history of HPV infection. The immune system will be stimulated by these vaccines which will result in specifically targeting and killing infected cells. The safety and efficacy of a therapeutic DNA vaccine are being tested by ongoing clinical trials to treat HPV related cervical and vulvar lesions [115–117]. A combination of preventive and therapeutic vaccine would be an ideal strategy in this case.

Topical microbicides is another preventive strategy which is being explored. In various studies, carrageenan which is an extracted compound from seaweed widely used in foods and other products has been reported to inhibit infection with HPV. Clinical trial in healthy individuals with a gel containing carrageenan is underway to test its efficacy to prevent genital HPV infections.

6.1 Immunization of the pregnant women

The response of the adaptive immune system of the infants cannot be protective to many pathogens in the first months of life. The T cells of both fetal and neonatal origin are shewed towards Th2 responses which are ineffective against intracellular pathogens. Ineffectiveness has also been reported for bacterial polysaccharides by antibody responses. Infants rely on additional protection during this period which is acquired from maternal antibodies during gestation passively transported through the placenta. At the time of birth, the antibody levels present in the infants

are correlated with the maternal antibody levels and the therefore, there is an interconnection between the antibody levels present in the maternal circulation and the degree of transfer of antibodies. However, the suboptimal maternal specific antibodies may not be sufficient to provide full protective immunity or can provide protection only for a limited period of time to the infants. Moreover, the maternal antibody levels decrease over a periods of approximately 6 months after birth. Therefore, the aim of the maternal immunization is to increase the concentration of maternal specific antibody and their passive transport to the fetus which will reduce the window of vulnerability for infants. IgG (Immunoglobulin G) is the only isotype among the five antibody classes that has the ability to efficiently cross the human placenta. Syncytiotrophoblast cells of the placenta, are responsible for the transfer of the IgG antibodies from mother to the fetus, which are located in contact with the maternal blood. In the circulation maternal IgG are internalized in endosomes and bind to Fc receptors (FcRn) of the neonatal cells which are expressed on the surface of the internal endosomes. On membrane of the fetal side of the syncytiotrophoblasts, the endosomes fuse and the IgG are released from FcRn. Passing through the villous stroma and fetal capillary endothelium, IgG enters the fetal circulation through an unknown mechanism. With the largest transferred proportion during the third trimester of pregnancy, the transfer of IgG through placenta increases over time especially within the last 4 weeks. Consistent with an active transport process, the IgG concentration in the fetal circulation are generally greater than the maternal circulation at full term of pregnancy [118, 119]. This transfer is influenced by several factors such as maternal non-infectious diseases, placental integrity, total maternal IgG concentration, FcRn availability, IgG subtype, timing of infection or vaccination and nature of the antigen [120]. IgG4, IgG3 and IgG2 are the least efficiently transferred to the fetus as compared to IgG1 which is the most efficiently transferred antibody subtype to the fetus.

Approximately after 2 weeks of maternal immunization, the concentration of specific antibodies starts increasing which suggests that if the vaccination is provided between 28 and 32 weeks of pregnancy, the optimal amount of specific IgG may be achieved in full-term infants at birth, but may not be the same for preterm infants. Diphtheria toxoid-acellular pertussis vaccine (Tdap) in the second trimester is reported to be reduced by the vaccination with tetanus toxoid which results in higher neonatal anti-pertussis antibody titers as compared to vaccination in the third trimester both in preterm and term neonates [121, 122]. The total longer transfer time may be a reason for the accumulation of antibodies in the fetal circulation. In addition to the maternal IgG antibodies which is transferred through placenta and known for providing protection, lesser concentration of IgG, IgM and high concentration of maternal IgA are also excreted in the breast milk and colostrum [123]. Immediately after delivery or in the second or third trimester of pregnancy, vaccination with Tdap reported to increase the pertussis-specific IgA antibody levels in the breast milk [124]. Therefore, another mode of transferring antibodies to the new born is breastfeeding. The maternal IgA transferred through the breast milk helps protecting the infants against enteric infections and respiratory illness with fever in infants born to influenza-vaccinated mothers for at least 6 months after birth [42, 123]. Though, there are evidences highlighting the maternal immunization benefits, few studies have also shown controversial interferences between the maternal IgG antibodies and the infant antibody responses [125].

The "immunological blunting", a phenomenon is observed after the primary vaccination series in early infancy when the maternal IgG antibodies can inhibit the immune responses against the same or related antigens. While after the booster dose, this blunting effect dissipates [119, 126]. Blunting has been reported to be observed with polio and measles vaccines after natural infection or maternal

immunization for maternal antibodies [119, 127]. Though, the clinical importance of this blunting effect is unknown, the epidemiological data of implemented maternal immunization from various countries have not shown any negative impact on the protection against the diseases targeted [26, 128].

6.2 HPV vaccination during pregnancy

Gardasil and Cervarix both HPV vaccines are recombinant which contains virus-like particles (VLP's) and enhanced by an adjuvant which is responsible for triggering an immune response higher than a natural infection [129]. Gardasil 9, a 9-valent HPV vaccine was only licensed for use in the USA in December 2014.

Depending on age, full coverage by the HPV vaccine is obtained by 2 or 3 doses with the first dose administered at time o, followed by the second dose after 1–2 months and the third dose after 6 months [130]. While, all doses are not received by many girls [131]. In order to achieve long-term duration of immunity, the repeat doses of vaccine are given which boost the immune system.

Worldwide, millions of doses of HPV vaccine since its introduction have been administered and involuntary administration also occurs during pregnancy as the young fertile women are the main recipients of the vaccines. Potentially harmful adverse effects (AE) to the unborn child such as preterm birth, miscarriage, congenital malformations, fetal death or fears of teratogenicity raise concern among both the health care providers and recipients. The development of sensitive organs such as the heart, the central nervous system takes place in the first trimester of pregnancy and in this period the environmental factors like medications and drugs theoretically might cause damage the developing fetus which is the main reason of concern. The vaccine manufacturers (Merck and GlaxoSmithKline) and the World Health Organization recommend avoiding HPV vaccination during pregnancy [36]. However, in case of accidental vaccination of pregnant women there are no interventions and no mandatory pregnancy testing before vaccination recommended so far. Moreover, conducting studies to investigate the pregnancy outcomes by administering HPV vaccines to pregnant women are not ethically feasible. In pregnancy, the true safety of the HPV vaccination has not yet been established through randomized controlled trial. Hence, the HPV vaccine administration to the pregnant women has not yet been approved [132].

7. Conclusion

In pregnant women, many observational studies reported the HPV infection risk but there are controversial results too. Higher HPV prevalence has been reported in few studies, whereas several studies reported lower prevalence in pregnant women or there is no statistical difference between pregnant and age matched non-pregnant controls [16].

For a successful pregnancy, a modulated, dynamic and responsive immune system is required but definitely not a suppressive one and this has been supported by an increasing number of studies. At the feto-maternal interface, the trophoblastic cells are important for the receptive immune system establishment which is achieved as a part of response mechanism to the normal microbiota which highlights the complexity of the regulatory pathways involved during pregnancy. Moreover, there are evidences on the effects that changed the modulated immune system and the receptive feto-maternal interface by a clinically silent viral infection emphasizes the necessity of better detection, treatment and prevention of the viral infections during pregnancy. This will further lead not only to the better outcomes

of pregnancy but also the postnatal development can be affected in a better way as these viral infections and the subsequent inflammations reported to be associated with mental health issues and diseases of the immune system such as asthma and allergies. The effects of viral infections on fetal development during pregnancy can more be exemplified by the recent Zika virus outbreak and its teratogenic effect on the development of brain [22]. Therefore, it is important to understand the complex immune responses during pregnancy, with the continued risk of pandemics and the emergence of newer diseases associated as secondary to the viral infection, which will lead to the development of appropriate approaches and tools to protect both the fetus and the mother [41].

Moreover, there are very limited data is available due to the very limited number of investigations have been performed on materials from spontaneous abortions and spontaneous preterm deliveries due to HPV infection and the heterogeneous study groups making it difficult to come to a reliable conclusion. A proper study design, selection of proper controls is very essential in this case and a strict control of the similarity in patients/samples is needed for a valuable comparison between studies. Furthermore, the simple detection of a virus cannot be a real causative role for diseases in general or adverse pregnancy outcomes. Therefore, for this particular situation it is important to study the cellular localization and the viral activity to come to a realistic conclusion.

Therefore, we recommend more investigations on materials of adverse pregnancy outcomes including spontaneous abortion and spontaneous preterm delivery and the molecular mechanism of HPV infections on it which is the need of the hour and researchers need to conduct new studies to clarify the exact molecular mechanisms involved on the HPV infection in early pregnancy and how the self-clearance takes place during the course of pregnancy.

Conflict of interest

The authors declare no conflict of interest.

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