Mechanisms by which the fetus survives in utero

Introduction:
The uterus fetal environment is sequestered from frequent pathogenic encounters due to which the defense system of the neonate if often immature and inexperience. It remains in a highly vulnerable stage in the first 6 weeks of life. Also, many components of the human immune system remain immature and not well developed. Despite all these limitations, the host fetal defense system is capable of active engagement and immune responses occur in the uterus when the fetus is challenged immunologically. Stem cells from the Yolk sac are the region from where the host immune system starts to develop initially. After, yolk sac the liver and the bone marrow take the responsibility of the development of the immune system. Natural Killer cells or NK cells and T & B lymphocyte precursor cells are present in the fetal liver at 6 weeks or 7-8 weeks of gestation. The fetal thymus is colonized by T-Cell precursors at 8-9 weeks and pre B cells found in the bone marrow at 13 weeks as evident from the attachment of cluster of differentiation or CD cells. (1)

Fetal growth inside the utero from an immunological point of view:
During the second trimester, there is an onset of mature T & B lymphocytes and complement component is detected from 6-14 weeks gestation and this level of lymphocytes are much lower than the adult. Polymorphonuclear leukocytes or PMN are the first identified cells in the fetal stage of the yolk sac during hematopoiesis. (2) Until 14 weeks of gestation, mature PMN's are not identifiable in the bone marrow or liver. (3) By 22-23 weeks, the PMN count increases but is only 2% of the circulatory PMN concentration as measured in the cord blood. However, it is compensated by highly proliferating hematopoietic progenitor cells which can be due to the shifting of the stem cells from the liver to the bone marrow.

Circulating monocytes do not appear in the fetal blood in less than 20 weeks of gestation and 70% of blood cells in the liver is composed of macrophages before this organ becomes the main site of hematopoietic activity. At around 30 week's time, monocyte concentration becomes 3%-7% of the circulating blood cells. Also, the influx of mononuclear phagocytes to the site of inflammation is delayed and attenuated in the newborn. The prenatal cell membrane expression of NK cells is lower than the postnatal types and this can explain the diminished cytotoxicity in vitro and vulnerability of the newborn to viral and parasitic infections. Complement proteins like the C4, C2, C3 and C5 is synthesized in early gestation between 8 to 14 weeks without any transplacental passage of complement components. Compared to classical pathway activity in both pre and term infants, alternate complement pathway activity is more diminished.

Fibronectin improves leukocyte function in vitro and aids in neutrophilic adhesion, chemotaxis and also assists in the killing of bacteria, yeasts etc. However, in vitro Fibronectin synthesis is decreased by macrophages in the neonatal period and in certain abnormal physiology due to different diseases like respiratory distress syndrome, sepsis, birth depression and IUGD. (4)
C-reactive protein (CRP) is synthesized by the fetus and the newborn and it helps to activate the classical complement pathway. Neonatal cord blood neutrophils are profoundly deficient in lactoferrin which helps in neutrophilic reactive oxygen intermediate production, chemotaxis, endothelial adhesion, and aggregation. (5) The human thymus development occurs as an outgrowth from the 3rd and 4th pharyngeal pouches between the 6th and 7th week of gestation. Lymphocytes which are destined to become T-cells appear in the epithelial cells in the 9th and 10th week's time. (6) The cortex and the medulla of the thymus develop around the 10th week of gestation and the Hassall's corpuscles appear at about 12th week. Undifferentiated cells entering the thymus do not possess CD4

or CD8 antigen but do express the T cell markers. (6) The thymus is the site where expression of CD7 followed by CD1, CD2, CD5 and somewhat a later CD3 expression occurs along with the maturation of the T-cells.
With increase in gestation, most cells leaving the thymus either express the CD4 or CD8 surface antigen. Cells lacking both the antigens CD4 or CD8 retain the stem cell function and possess a receptor (CD25 Tac antigen) for IL2 which plays an essential role in promoting simultaneous appearance of CD4 or CD 8 antigens.

During the 12th week intra-uterine life in the fetus, CD 3 positive cells can be identified in the peripheral blood, and by 22nd week of gestation it represents more than 50 % of T Lymphocytes. These CD 3 positive cells also express either the CD4 or the CD8 antigen. By the 13th week of gestation CD3 positive cells appear in the fetal liver or spleen and by the end of the second trimester represent more than 50 % of the T lymphocytes in these organs. The T-cell helper/ suppressor ratio (CD4/CD8 ratio) in the cord blood is approximately 1.7:1 against the adult ratio of 2:1. In the peripheral blood 20 % of the T cells express thymocyte antigens compared with less than 1 % expression in the adult [7].

In early gestation, functional responses involving the T lymphocytes and T cell derived lymphokines can be demonstrated. By the 12th week of gestation, lymphocytes obtained from the human thymus respond both to mitogens and to foreign histocompatiblity antigens as observed through in mixed lymphocyte culture. [8] B cell maturation occurs normally in two stages. In the first stage undifferentiated stem cells mature into cells identifiable as B lymphocyte which is antigen independent phase taking place in the fetal liver and the bone marrow [9].

The second stage of lymphoid differentiation is antigen dependent and during this phase B lymphocytes are transformed into plasma cells. The first recognizable cell in the B cell lineage is the pre B cell and can be detected in the fetal liver on the seventh to the eighth week of gestation. The presence of heavy chain IgM could be seen at this stage. (10) As gestation progresses, pre B cell can be detected in the fetal bone marrow also. It is at the pre-B cell stage of development that clonal diversity is imitated. Intact immunoglobulin genes are formed by the rearrangement of gene segments comprising each heavy and light chain family. Pre-B cells also give rise to immature B lymphocyte which expresses only surface IgM and complement receptors [11]. These cells could be detected in the fetal liver at 8–9 weeks of gestation. However, clonal anergy could be noticed in the case of exposure to self-antigen. By the 12th week of gestation cells that express another immunoglobulin IgA or IgG appear. At a somewhat later stage, the mature B cell stage, cells express membrane bound IgG or IgA in association with the membrane IgM or IgD and by the 12th week of gestation, the normal fetus has levels of circulating B lymphocytes that are equal or higher than the adult. Fetal B lymphocytes can be demonstrated in highest proportion in the spleen about 30 %, blood 35 % and lymph nodes 13 %.

The fetus acquires the ability to produce serum immunoglobulins early in gestations [12].By the eighth week through in vitro studies the ability of fetal cells to produce antibody (IgM) was demonstrated. The synthesis of IgG synthesis appears a slightly later and IgA synthesis begins at about 30 weeks of gestation. However due to the sterile environment of the uterus the inability of the fetus to respond to certain kinds of antibody, T cell suppression and B cell differentiation results in a very little antibody level before the time of birth, therefore, making the fetus immature immunologically[13]. At the time of birth, most of the circulating antibodies in the fetal system are

IgG antibodies which pass through the placenta. Less than 10% of fetal IgM levels are demonstrable at term gestation and by 1-2 years of age, it reaches the adult level. The adult level of IgG is attained at 4–6 years and adult IgA is attained at puberty.

B lymphocytes are present in the fetus by the end of the first trimester; however there is very little active fetal immunoglobulin production during this time. At 20-22 weeks of gestation, the levels of fetal serum immunoglobin are extremely low. During this time an accelerated active transport of IgG takes place across the placenta [14]. Only the maternal IgG is transported due to the presence of specific placental receptors for heavy chain IgG molecules and this active transport of IgG causes its rise in concentration in the fetus by 5–10 % higher than the mother. Elevated levels of IgM or IgA in the cord blood demonstrates that the infant has been exposed to an antigen in utero and has synthesized and the capacity to produce antibody itself. Congenital infection with syphilis and rubella characteristically produces the elevation of the cord blood IgM concentration. Elevated levels of both IgM and IgA also may be found if there is the transplacental materno-fetal hemorrhage.

Fetal survival inside the womb without rejection:

A successful pregnancy happens when the maternal immune system that may aid in the rejection of the fetus is shut off in the uterus which is not the case in recurrent spontaneous miscarriages as the immune camouflage and protection are not initiated due to the decrease in the cell-mediated immunity and increase in the humoral immunity.(15) It has been found that the introduction of a Rh antibody in a Rh negative mother carrying a Rh positive fetus prevents the maternal immunity from recognizing and rejecting the baby's Rh positive cells. The mother receives signals from the uterus in forms of hormones which are endocrinal in nature and other paternal genetic information some of which are the HLA antigens that the father gives to the child. Appropriate mismatch of the parents leads into the maternal system recognizing the cells of the fetus or trophoblasts which further forms the placenta as foreign material. The lymphocytes which congregate in the mother's uterus communicates with the molecular messages from the baby's cells and begins to protect the baby from getting rejected. As early as 5 months of pregnancy, the maternal antibody can be detected which attaches itself on the fetal cells thereby camouflaging these cells from the mother's immune killer cells which can have the ability to destroy the fetus. Also, this attachment of specific antibodies to the baby's cells brings in with a molecular signal which helps the fetus to grow and divide. Without this growth signal, the baby and the placenta regresses. (16) The maternal antibody production should be high which if not otherwise can lead to rejection of the fetus and the cells of the placenta will not be stimulated to grow. By HLA typing, these couples can be referred to as like brothers and sister or inbred rather than two distinct individuals. In summary, it can be inferred that the message from the father also is not heard by the mother leading to an absence of immunoprotection of the fetus and ultimately into fetus rejection. (17)

Alteration in the blood clotting mechanisms is another problem that interferes with a subsequent pregnancy success. Each loss in pregnancy is associated with an approximately 20 % increased chance of production of an autoimmune response to fatty molecules called phospholipids which are integral parts of the baby's cells. Cardiolipin is one of the best known and most tested phospholipids for the heart fat. (18)

Cardiolipin or one of its 'brothers' and "sisters" in the mother, may activate and speed up her blood clotting in the vicinity of early pregnancy resulting in loss of the fetus. Also, pregnancy related problems in the neonate can occur in the form of intrauterine growth retardation, toxemia, and

even intrauterine fetal demise. Half of these will be premature and the other half will have features of growth retardation, the remainder of the babies will possibly die during pregnancy due to abnormalities of the anti-phospholipid antibody and a demonstrated clotting abnormality (i.e., the lupus anti coagulant) [19]. Other causes of recurrent spontaneous abortion include hormonal problems, abnormal development or diseases of the uterus or cervix, poor sperm quality, infections, chromosome abnormalities and chronic diseases.Every person's white blood cell type (tissue type, HLA type) consists of ten numbers, half of which comes from the mother and the father. These white blood cell numbers are molecules or molecular antennas that are present on the surface of the person's white blood cells, and play an important role in immune system processes against foreign pathogens. (18)

Sixty percent of the first-born children of secondary couples are DQ 0501/501 (formally called DQ 4.1 homozygous). This means that they are pure bred with regard to this part of their white blood cell type as both mother and father contributed the same 4.1 genes. Analysis of several hundred lives born children who were born following immunological treatment of their mothers revealed no live-born DQ 0501/0501 babies. Women whose first babies are DQ 0501/0501 are at high risk of making an autoimmunity response which involves the production of an antibody in their body that attacks the phospholipids important in building the placenta of the baby. They are also prone to increase the numbers of natural killer cells in their blood from 4 % to over 20–30 % [17]. Further studies in the laboratory by Prof. Alan Beer in 1995 showed that this type of natural killer cells in women with the recurrent miscarriage can also damage the early cells of the bay that will make the placenta. [20]
Treatments can be designed to counter one or two types of immunological problems which can result in a destruction of the placenta, embryo or fetus by antibodies produced by the pregnant woman. Alan Beer suggested one such approach to block antibodies against the fetus by the mother's own tissues. In the language of Prof. Beer, 'Blocking antibodies create a disguise and the fetus becomes a wolf in sheep's clothing as far as the mother's immune system is concerned' [17, 21, 22].

With a better understanding of the pathophysiology of pregnancy, it can be revealed that highly specific, protecting systems operate during pregnancies that do not interfere with any of the mother's immune responses. A pregnant woman if she receives a kidney from an unmatched donor, she would reject it at any other time similar to fighting off outside infectious agents [23,24,25,26]. However, such is not in the case of pregnancy due to the presence of this blocking antibody and creating an immunological fortress for the fetus in the maternal system which supposedly comes from the other half or the father who is again a foreigner to the mother's immune system. Therefore, nature does not rely on the mother alone to protect the fetus. As indicated by another set of studies, the substance that stimulates the production of blocking antibodies comes from the father, carried in by the sperm that produces the pregnancy [27].

Dr. JYH Kwak et al. [28] and Prof AE Beer et al. [20, 29, 30] have however, indicated that in certain cases if the tissue of the father and the mother are too much similar immunologically, the mother's body may fail to respond adequately to the father's feeble signal to produce blocking antibodies. (31) This results in outright rejection of the pregnancy tissue or failure of the fetus to thrive. Normally, the signal to produce blocking antibodies comes from the paternal contribution to the embryo. The antibodies can be measured as early as 5 weeks of pregnancy. But if the maternal and paternal tissue types are too similar the signal is not received and the pregnant woman does not produce the protective antibody [32] Also mice model results show that Th2 play a more important

role than Th1 and suggest that a simple immune-endocrine network is involved in establishing the characteristic Th1/Th2 balance observed during pregnancy [33] Alloimmunisation, which is known to prevent resorptions in this abortion-susceptible combination and to prevent TNF- or LPS-induced abortions/resorptions, enhances the placental production of IL-4 and IL-10 in CBA × DBA/2 mice matings.

Furthermore, recombinant IL-10 given alone by intraperitoneal injection has shown to completely reverse the high incidence of fetal resorptions, in control to anti IL-10. Antigamma IFN and pentoxifylline (an anti-TFN agent), which partially reduce resorption, act in synergy for optimal fetal protection. Injection of recombinant bovine trophoblast protein corrects the high rate of fetal resorption in CBA × DBA/2 mice and is correlated with increased placental IL-4 and IL-10 production. The results of many studies indicates that non-specific killer and inflammatory cells, cytostatic and cytotoxic lymphokines play a crucial role in immunologically mediated fetal death in both naturally abortion-prone CBA×DBA/2 and B10×B10. Activation of GM1 positive cells by poly-IC or gamma IFN lead to abortion [15, 34, 35]

TJ6 is another novel immune suppressor protein that can induce apoptosis also. Early mice model studies demonstrated that mice treated with antibody to the TJ6 protein early in pregnancy resulted in ablation of those pregnancies. The gene for TJ6 was subsequently cloned in both man and mice and was found to be nearly identical. Further flow cytometric analysis of TJ6 on peripheral blood lymphocytes of pregnant women revealed that TJ6 was expressed on CD19 positive B cells. Specifically, TJ6 is expressed as a 45 kD membrane form on the surface of these cells with the initial protein showing to be approximately 70 kD in length, two additional forms have been identified. Subsequent studies show that the TJ6 is post-translationally modified to produce a 45 kD membrane form and an approximately 18 kD soluble form. Some preliminary studies have shown that the membrane form is involved in programmed cell death of the cells expressing it. The soluble form appears to be involved in anti-proliferative effects of anti-CD3 and allogeneic stimulated cells [36] Also, there are 30 different types of white blood cells or Lymphocytes of which, however, eight of them are most important and can be assessed by flow cytometry tests designed by Prof. Alan Beer. (28) Disorder of these eight cell types may predict a future pregnancy loss.

The presence of CD3 or Pan T cells ranges between 63 % and 86 % and are low when the immune system is suppressed and vice versa. CD4 or T Helper cells range between 31–53 % and are destroyed by HIV virus. If they are low the etiology of the deficiency must be studied. CD5 or T-cytotoxic suppressors have a range in between 17–35 % and they coordinate a strong or weak immune reaction by coordinating Pan T and helper T cells. CD19 or B cells range is between 3–8 %. These lymphocytes are plasma cells that produce antibody IgG in the lymph system and lastly, the IgA which infers organ immunity. CD19 is high in cases of women with an immune-related cause for infertility

Further CD56+CD16+Natural killer cells, a range is between 3–12 % which is produced in the bone marrow and produces tumor necrotic factor. If it varies above 18 %, intravenous immunoglobin may help the situation, otherwise, may result in reproductive failure. CD56+Natural killer cells like the previous one have also the same range between 3–12 %. They lack CD16 molecules or rather, known as CD56+CD16- natural killer cells, which could be identified in decidua and may also produce the large quantity of tumor necrotic factor in the decidua and can kill placental cells. A level of 18 % or above predicts poor pregnancy outcome and may necessitate I.V. Immunoglobin G therapy which can decrease the killing potential of the natural killer (NK) cells. CD3 IL-2 R cells have a normal range of 0–5 % during pregnancy. They are high in autoimmune disease in case of organ rejection specifically kidney and bone graft. If the level is above 10 % I.V. immunoglobin may prevent its activation. CD19+CD5+ or B1 cells, ranges between 0–3 percent. When activated they produce

antibody against hormone, hormone receptor, and neurotransmitters and may also justify autoimmune condition or rejection of an organ, e.g., bone marrow. [20]

History of understanding fetomaternal tolerance:
Little in 1924 first gave an idea to this incredible thought that how the mother is able to tolerate the fetus inside her womb leading him to propose that the embryo might have no definite physiological characteristics which as individual are not enough to be recognized as foreign by the maternal immune system.

In 1932, Witebsky and Reich suggested that the trophoblastic layer of the fetus might be nonantigenic and can be acting as a barrier between the mother and fetal system. However, it was in 1953 when for the first time, Medawar postulated the now famous "Medawar paradox" that the lack of fetal rejection by the mother's immune system might be principally due to three basic and important reasons which are 1. The presence of an anatomical barrier between the mother and the fetus like the trophoblast layer, 2. The fetus is immunologically immature and 3. The maternal immune system might be immunological inert. (5) However, Medawar's theory lacked certain aspects related to another site specific immune suppression mechanisms.

However, Medawar's first theory was seriously challenged when a bidirectional exchange of fetal and maternal cells through the as supposed barrier tissue at that time was demonstrated. Fetal cell microchimerism was originally demonstrated in mice models along with its long-term persistence in the bone marrow of these animals. (6) Further it was shown through various mRNA transcript methods in the peripheral blood that the fetal cells can enter the maternal circulation as early as 6 weeks of gestation and can persist in maternal blood for decades even after the termination of pregnancy without any sign of graft versus host syndrome although data concerning the health consequences of persistent fetal cells in the maternal tissues are still contradictory as it was seen in auto immune mothers there was a higher concentration of fetal microchimerism.(8) However, until now there is no definite scientific data or concrete evidence to directly co-relate the fetal cells in auto immune disorders of the mother. (9, 10, 11, 12, 13) as fetal chimerism is also observed in the peripheral blood of healthy individuals. (8, 14). Further studies have also demonstrated that fetal chimerism in the maternal system can help in immune surveillance for malignant cells as observed that in most breast cancer women fetal microchimerism is reduced. (15, 16, 17) Also, Multilineage differentiation potential of fetal cells which have been transferred to the mother has been shown suggesting the fact that these cells might aid in tissue regeneration of the mother also. (15)

Medawar' second hypothesis that is the fetus is immunologically immature was also challenged when the expression of fetal MHC I and MHC II antigenically matured was observed and detectable in the maternal circulation. (18) Also it was thought that the trophoblast layers which lack matured MHC class I and class II molecules and in contact with maternal circulation can have the ability to evade detection and destruction by the maternal cells which was later refuted due to the fact that the trophoblast population which were in contact with the maternal deciduas do in fact express the MHC Class I molecule. (19, 20) Further by Shomer and Rogers observed that expression of allogeneic MHC class I molecules on various trophoblast cells does not show any increase in fetal loss even in the presence of defects in the Fas/FasL pathway. (21, 22)

The third hypothesis of Medawar pertaining to the lack of immune expression by the mother was also refused after it was shown that the maternal immune system can recognize fetal cells and even it can reject fetal tissues as observed in pregnant rats. (23) Also, it was observed that the maternal immune system is able to attack the pre-implantation blastocyst when the zona pellucida is

removed. (24) Maternal T cells do respond to fetal antigens during the time of pregnancy but the nature of the immune response appears to vary during gestation as demonstrated by various conflicting results. (25, 26, 27, 28) Also, the production of alloantibodies to paternal antigens has been reported and while the increase in the alloantibody production happens with subsequent pregnancies, it, however, does not affect the outcome of the pregnancy. (29, 30)

Newer Hypothesis:

Role of HLA-G and other minor HLA

Thus came the new era where different local mechanisms were suggested by which the protection of the fetus from the mother's immune system was proposed. Still, it is not clear that how does the fetus survive inside the mother for 9 months. The most well-known mechanisms are 1.Expression of nonclassical MHC molecules by the trophoblast layers like HLA-E, HLA-F and HLA-G and the function of HLA-F is still unknown. 2. Expression of the IDO enzyme by the placental cells resulting in the deletion of tryptophan and kyurenine production. 3. FasL expression by trophoblastic cells 4.Expression of complement regulator proteins by trophoblast and decidua cells. HLA-G can help in the protection of the fetus against T-cell and NK cell mediated as observed through mixed lymphocyte reaction or MLR. (37, 38) HLA-G can also induce apoptosis of lymphocytes through Fas/FasL pathway. (39) HLA-G activity is not direct and it works through HLA-E on the trophoblastic cells by the stabilization of the HLA-E expression on the cell surface and allowing the CD94-NKG2 inhibitory receptor to bind on the maternal NK cells leading to inhibition of the NK cell activity. (40, 41) Also, HLA-G interacts with dendritic cells through KIR-related leukocyte-like Ig-like receptors which can have an indirect effect on the maternal T and NK cells and thereby facilitate the T regulatory cells. (42, 43)

Role of Indoleamine-2, 3-dioxygenase (IDO)

Munn and Mellor suggested evidence that placental cells or trophoblasts can synthesize this tryptophan-catabolizing enzymes also known as Indoleamine 2, 3-dioxygenase or IDO and can provide protection from T-cells by inhibiting the synthesis of tryptophan which is an essential requirement for T cell activation or by catabolizng the enzyme as studied in both in vitro models. Further in mice models, it was shown that depletion of this IDO enzyme leads to fetal allograft rejection also. (44, 45, 46) This catabolising effect on the tryptophan enzyme can also inhibit the function of NK cells, T and B cells. (47) In IDO knockout studies, it was further observed that presence of another enzyme tryptophan-2,3-dioxygenase can promote tryptophan catabolism and can compensate for the loss of activity of IDO activity during gestation.(49) IDO can also affect the functioning of dendritic cells thereby preventing T-cell regulation. (50) However, the role of Trytophan as a catabolic enzyme is still less clear in the case of human pregnancy as IDO deficiency has not reported in any pathological cases during human pregnancy.

Fas/FasL:

Also the presence of Fas/FasL at the maternal decidua and the fetal tissues can also mediate apoptosis at the maternal-fetal interface throughout gestation. (56, 57) However, recent reports have suggested that there might be a more complex role involved in this death ligand receptor mediated maternal tolerance as this mechanism might help in allograft rejection rather than survival. (58, 59)

Role of Complement:

The role of complement can be also highlighted in the feto-maternal tolerance as it is a component of the natural immunity. It is believed that the complement system during pregnancy is tightly regulated in order to protect the fetus from inflammatory associated damages and inducing feto-

maternal tolerance. It can be activated via pathogens and also after transplantation of allogeneic and xenogeneic cells resulting in the production of inflammatory cell chemotaxis and enhanced phagocytosis and cell membrane lysis by membrane attack complex or MAC. Further in animal studies, it was demonstrated that the Crry gene prevents deposition of the C3 and C4 complement pathways thereby preventing the initiation of the complement pathway at the fetomaternal interface. (62, 63) Deficiency of this Crry gene results in gestational failure in mice. In humans, unlike mice, a number of complementary proteins are produced at the fetomaternal interface like DAF, MCP and CD59 and its role in the C3 complementary cascade has also been demonstrated. (65, 66) The trophoblastic cells of the fetus may also encounter and confer resistance to the invading antibody and compliment activated molecules which are quite analogus to organ transplantation. (67)

Further characterization studies involving different leukocytes present at the fetomaternal border either at the trophoblastic layer or decidual level is also an important area of research pertaining to fetomaternal tolerance of the fetus. Cells isolated from the amniotic and chorionic membranes have shown not to induce any allogeneic or xenogeneic T-cell responses and can actively suppress T-cell proliferation. (76, 77) Also, both human amniotic membrane and human amniotic epithelial cells have shown to survive for prolonged periods post transplantation in immune-competent animals like rabbits, rats, guinea pigs and monkeys along with long-term engraftment after the intravenous injection of human amniotic and chorionic cells into newborn porcine, rat models. These models also showed human microchimerism detected in several organs thereby suggesting a tolerogenic potential of these pregnancy-specific biological substances cellular products. (76) Further several animal models have shown the safety and efficacy of rat-derived amnion cells along with long-term survival without any visible graft versus host rejection, tumor formation or immunological rejection after in utero transplantation in rodent brain. (82) Recent investigations have also shown that the stromal layer of the amniotic membrane consists of two distinct subpopulations of cells which differ in their expression of HLA-DR, CD45, CD14, CD86, cd11B and which possess either T-cell suppressive properties or stimulatory properties. (83) However, their roles in controlling the fetomaternal tolerance are yet to be clarified in details.

History of fetomaternal tolerance:

Little in 1924 first gave an idea to this incredible thought that how the mother is able to tolerate the fetus inside her womb leading him to propose that the embryo might have no definite physiological characteristics which as individual are not enough to be recognized as foreign by the maternal immune system. (37) In 1932, Witebsky and Reich suggested that the trophoblastic layer of the fetus might be nonantigenic and can be acting as a barrier between the mother and fetal system. However, it was in 1953 when for the first time, Medawar postulated the now famous “Medawar paradox” that the lack of fetal rejection by the mother’s immune system might be principally due to three basic and important reasons which are 1. The presence of an anatomical barrier between the mother and the fetus like the trophoblast layer, 2. The fetus is immunologically immature and 3. The maternal immune system might be immunological inert. (38) However, Medawar’s theory lacked certain aspects related to other site specific immune suppression mechanisms.

However, Medawar’s first theory was seriously challenged when a bidirectional exchange of fetal and maternal cells through the as supposed barrier tissue at that time was demonstrated. Fetal cell microchimerism was originally demonstrated in mice models along with its long-term persistence in the bone marrow of these animals. (39) Further it was shown through various mRNA transcript methods in the peripheral blood that the fetal cells can enter the maternal circulation as early as 6 weeks of gestation and can persist in maternal blood for decades even after the termination of pregnancy without any sign of graft versus host syndrome although data concerning the health consequences of persistent fetal cells in the maternal tissues are still contradictory as it was seen in auto immune mothers there was a higher concentration of fetal microchimerism.(40) However, until

now there is no definite scientific data or concrete evidence to directly co-relate the fetal cells in auto immune disorders of the mother. (41, 42, 43, 44, 45) as fetal chimerism is also observed in the peripheral blood of healthy individuals. (40, 46). Further studies have also demonstrated that fetal chimerism in the maternal system can help in immune surveillance for malignant cells as observed that in most breast cancer women fetal microchimerism is reduced. (47, 48, 49) Also, Multilineage differentiation potential of fetal cells which have been transferred to the mother has been shown suggesting the fact that these cells might aid in tissue regeneration of the mother also. (47)

Medawar's Hypothesis:

Medawar' second hypothesis that is the fetus is immunologically immature was also challenged when the expression of fetal MHC I and MHC II antigenically matured was observed and detectable in the maternal circulation. (50) Also it was thought that the trophoblast layers which lack matured MHC class I and class II molecules and in contact with maternal circulation can have the ability to evade detection and destruction by the maternal cells which was later refuted due to the fact that the trophoblast population which were in contact with the maternal deciduas do in fact express the MHC Class I molecule. (51, 52) Further by Shomer and Rogers observed that expression of allogeneic MHC class I molecules on various trophoblast cells does not show any increase in fetal loss even in the presence of defects in the Fas/FasL pathway. (53, 54) The third hypothesis of Medawar pertaining to the lack of immune expression by the mother was also refuted after it was shown that the maternal immune system can recognize fetal cells and even it can reject fetal tissues as observed in pregnant rats. (55) Also it was observed that the maternal immune system is able to attack the pre-implantation blastocyst when the zona pellucida is removed. (56) Maternal T cells do respond to fetal antigens during the time of pregnancy but the nature of the immune response appears to vary during gestation as demonstrated by various conflicting results. (57, 58, 59, 60) Also the production of allo-antibodies to paternal antigens has been reported and while the increase in the alloantibody production happens with subsequent pregnancies, it however does not affect the outcome of the pregnancy. (61, 62)

Accommodation:

The term "Accommodation" in organ transplantation is often referred to as the resistance of a graft to injury by the host's immune system. This concept was developed during the 1980'2 as an explanation for the unanticipated survival and well being of organ transplanted across ABO blood group barriers. (63, 64) Organs transplanted across blood group barriers usually undergo 75% of early and severe graft rejection or failure within 3 months of transplantation. (65) However removal of anti-blood group antibodies from recipients or if the binding of these antibodies are blocked the chances and prospects for long term survival and function of the graft increases like that of grafts matched for ABO glycoprotein. (66)

In the case of pregnancy, the main question lies how a fetus where half of the HLA's come from the mother and father persists and tolerates itself in the mother's uterus for 9 months without any rejection. This finding has further lead to the concept and idea of accommodation which if not present could result in a toxic assault by antibodies of the recipient and complement activation. (67) This is the same case observed during fetal tissue research in regenerative medicine where the fetal tissue survived in Parkinson's patient for more than 10 years without any rejection and considerable changes.

Mechanisms of Accommodation:

Accommodation can reflect heightened control of complement activation such due to which sub toxic complements are activated rather than acute toxic amounts of complement protein upon the binding of the anti-graft antibodies. A study by Dalmasso et al., revealed that due to hyper

expression of CD59 after complement activation on endothelial cells, killing of cells by terminal complexes is inhibited.(68) Williams et al., also further showed that for a given amount of antibody binding, accommodating organs activate less complement components than rejected organs.(69) Koch et al., showed that heaptocytes which like an accommodated organ can resist complement mediated killing and exhibit an intrinsic inhibition at the C3 and C4 level. (70) At the molecular level, NF-Kappa Beta activated by complement system and cytokines can induce the transcription of IkappaBeta which can inhibit the function of NF-Kappa Beta, preventing apoptosis and injury by a range of potential toxic substances. Also the function and presence of protective genes can provide accommodation as it has been found that complement and other noxious factors can induce the activity of hemeoxygenase-1, anti apoptopic proteins like Bcl-2, A20, and the PI3K-AKT pathway. (70)These all together can prevent cell apoptosis. (71)

Therefore the concept of accommodation shifts the whole view of immunity theories and tolerance. (72) Indeed, both accommodation and tolerance can explain how immunity avoids autotoxicity, and both might be integral to Ehrlich's concept of horror autotoxicus. (73) In another terms, accommodation in the fetus and fetal tissues helps them to get accustomed to toxic cells and substances generated by the maternal auto immune system response.

Immunity to the Fetus

Fetal cells and tissues are normally found to be less immunogenic than mature cells and tissues [74],but still, it can elicit immunity in the mother.(23) Fetal antigens, particularly derived from the paternal histocompatiblity antigens, elicit humoral and cell mediated immunity in the pregnant female. (75) Indeed, the sera of previously pregnant women provide a useful source of antibodies specific for major histocompatiblity (MHC) that can help in accommodating the fetus during pregnancy. Mothers with the previous history of pregnancy are usually found to be more likely to have future successful pregnancies than those mothers who never had any pregnancy, suggesting that sensitization during or after pregnancy does not necessarily harm the fetus by immunological means (75, 76). Prior sensitization may have an impact on the size of the fetus and placenta (77) , both sometimes found to be larger. A female can be repeatedly sensitized to paternal antigens without any harm to the status of the fetus carrying the sensitizing antigens (78). While sensitization has been associated with spontaneous abortion and preeclampsia, these events are relatively infrequent. Therefore, either the fetus is protected from the immune response, perhaps by the placenta and/or by circulating blocking factors. (79) It can be also that the fetus and/or the placenta can resist injury inflicted by the antibodies and cells that can penetrate the trophoblast layer or the protective barrier.

Transplants, like pregnancy, induce both cellular and humoral immune responses and the degree of impact of these responses, however, depends profoundly on how the transplant receives a vascular supply. Transplants which consist mainly of cells and free tissues are vascularized by blood vessels originating along with the transplant recipient and are mainly susceptible to cellular rejection. (80,81) For any transplant, antibodies specific for cell and tissue transplants may be produced in large amounts; those antibodies penetrate poorly through the recipient vasculature and can have access to only small amounts of complement and effector cells residing in extracellular spaces. In cases of xenograft including cell and tissues, these transplants are highly susceptible in vitro to killing by xenoreactive antibodies. (82)

Similarly T lymphocytes, can, migrate actively through the recipient blood vessels to reach the target organ composed of cell and tissue allografts and in so doing can initiate and mediate cellular rejection. Also in organ transplants, the cells and tissues are fed by blood vessels of donor origin, and

these vessels can be readily targeted by donor-specific antibodies in the circulation and by complement pathway. As a result, organ transplants are highly susceptible to various types of antibody-mediated rejection. (80, 81) If the circulation of the recipient contains antibodies against the transplant at the time of reperfusion, those antibodies can bind and activate complement and cause immediate destruction of the graft. (83) This is also known as hyperacute rejection.

Also, Antibodies produced after the transplant if perfused by the blood of the recipient can also cause devastating but somewhat less dramatic injury. (84) This type of rejection, variously called antibody-mediated humoral or acute vascular rejection causes destruction of the graft in days to weeks unless intensive therapies, such as plasmapheresis, are instituted. (85) The circulatory system of the fetus for most of the part is quite distinct from that of the maternal circulatory system. Although there is enough evidence to prove that there is some exchange of cells through the mother and the fetus and vice versa. Antibodies like IgG which can often mediate hyperacute and antibody mediated rejection and is produced by the mother can pass into the fetus via the placenta. However some antibodies like IgM do not. (85) However even after the passage of IgG in the fetus, the fetus is not rejected also, therefore, denoting a point that the fetus is resembled as an organ than a tissue transplant. Also, the fetus might be targeted by alloreactive T cells and antibodies especially from mothers previously sensitized by paternal antigens. However, the effect of these maternal T cells can be locally suppressed or blocked by the trophoblastic layers via different mechanisms. Also, it is believed that T lymphocytes which reach the placenta may be active but within the placenta, they might become inert in the sense that they do not exert cytotoxically or other effector properties thereby resulting in the decrease of migration of these cells. Also, it might be that the T cells are deleted in some cases via the CD95; however, this deleterious mechanism might not be active in most parts since the mother does not become tolerant to fetal paternal antigens as shown in experimental models. Also, work with embryonic stem cells has shown the possibility that TGF-Beta locally produced might suppress the immunity. (86) This action of TGF-Beta and perhaps other factors allows semi-allogeneic and in some cases fully allogeneic grafts of embryonic stem cells to survive in a dose dependant manner like smaller doses of embryonic cells more prone to immune reaction compared to larger doses of embryonic cells as larger doses produce more TGF-Beta which has the capacity to suppress the host's immune system. However, the function of embryonic stem cells in the fetus and fetal tissues presents a mechanism by which it can evade the maternal immune system is still unknown.
Also, at the same time maternal immunity is important as it can infer a passive immunity in the fetus till the fetus becomes matured enough to generate its own humoral immune response. However, in some cases transfer of maternal antibodies to the fetus can result in deleterious effect on the fetus leading to cellular injury, lysis of erythrocytes, apoptosis. Further antibodies directed against Rh positive antigen can cause fetal erythrocyte lysis leading to extreme heart congestion and failure. (87) In pregnant rat models, sensitized with nerve growth factor or NGF amount an antibody response with respect to an antigen has shown to get transfer into the fetus leading to the destruction of the peripheral nerves. (88) Complement is available in the human fetus since the second trimester and they do not cross the placenta but rather originates from the fetal cells and potentially destroy fetal cells. (89, 90) Armed with complement system, if the maternal antibodies can reach the fetus, then humoral injury to the fetus might be possible. Also this is possible due to the amplification of the maternal antibodies against the paternal MHC coded antigens, yet anti-HLA antibodies are still detected in the fetuses without any issues to the fetal health. (91)

Soluble forms of cell associated antigen can also block the binding of alloreactive antibodies as previously shown through in vitro and in vivo experiments. (79) However, the substantial amount of antigen binding to the antibody is also required. Failure of production of even one antigen can prove to be fatal for the fetus as it can produce death and humoral injury. Genetic modifications of the MHC genes can change the level of the MHC expression has reported to not have a profound effect

on the fetal survival. It has been found in some cases that antigens can enhance the growth of tumors rather than retard it. (92, 93, 94)This phenomenon is called enhancement, therefore, enhancing antibodies can protect grafts of normal tissue sometimes indefinitely by blocking immunological recognitions. (95, 96) This importance of enhancement in pregnancy was suggested in animal models whereby mice were mated with allogeneic strains better retain tumors and skin grafts from the allogeneic strain. This observation gave rise to the concept that the blocking of paternal antigens by alloreactive antibodies might explain the failure of the maternal immunity to injure the fetus. Thereby it can be concluded that the low expression of histocompatibility antigens would prefer both enhancement and blocking. (97, 98) Cryoprotection is also another phenomenon by which the fetus survives inside the uterus by means of various cellular and protective agonists. Both heme oxygenase-1 and Akt/PI3K pathways are implicated in accommodation process of the fetus. (99)

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