CHAPTER 3

SCIENTIFIC LITERATURE SEARCH

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Chapter 3: Scientific Literature Search

In chapter 1, we have seen that high-risk pregnancies are on the increase and the incidence of common complications of pregnancy have dramatically increased in common years. There are many factors that seem to contribute to these complications. Lifestyle and psychosocial stress have been shown to play an important role in their etiology. Stress management techniques can complement the present conventional management measures to further reduce the health risks to the mother and her child. There is now mounting evidence that yoga can reduce stress substantially. In this chapter, we review the scientific data in the literature that provides a rationale for conducting this study of yoga in high-risk pregnancy.

3.1 Etiology of Pregnancy Complications

The etiology of most pregnancy complications is still not clear. There are several hypotheses on how these complications originate and evolve. Maternal constitutional factors, such as immunological maladaptation and genetic predisposition are believed to lead to abnormal placentation, which in turn results in endothelial dysfunction and ultimately manifestation of pregnancy complications. Figure 3.1 provides an schematic view of this hypothetical process. In addition, it has been shown that a number of other factors play a strong role in the etiology of pregnancy complications investigated in this study. These include: increased insulin resistance and associated elevations in the levels of insulin, elevated levels of free fatty acids and triglycerides, increased oxidative stress, presence of microvillus particles and other cytokines in maternal blood, and finally imbalances in maternal hormones, such as progesterone, estrogen, and Lactogen.

Figure 3.1: Etiology of Pregnancy Complications

Maternal Constitutional Factors:
- Immunological Maladaptation
- Genetic Factors

Abnormal Placentation
Lifestyle Factors

Endothelial Dysfunction & Release of Placental Hormones

Pregnancy Complications (Clinical Symptoms)
3.1.1 IMMUNOLOGICAL MALADAPTATION

Pregnancy has been defined as a state of “altered immune competence”. While inflammatory response and hemostasis are innate immunological responses of human body to foreign insults, maternal immunity undergoes subtle alteration in order to tolerate the embryo and maintain proper defense against potential pathogens. Immune maladaptation and hemostatic imbalance have been suggested to be responsible for adverse pregnancy outcomes, including preeclampsia, preterm delivery, and IUGR. Improper placentation and shallow cytotrophoblast invasion have been implicated for this immunological maladaptation that leads to these complications, particularly preeclampsia. Preeclampsia is most prevalent among women in their first pregnancy and those of extreme ages. But interestingly, pregnancy in multigravidae by a new partner have a risk of preeclampsia close to the women in their first pregnancies. This seems to support the hypothesis of ‘immunological maladaptation’, wherein the maternal immune system fails to properly handle the new paternal antigen. The hypothesis is also supported by observations that the risk of preeclampsia is reduced when the partners have had a longer period of sexual intercourse prior to conception and that the risk is increased when partners use contraceptives that limits the female from exposure to semen. It has been shown that the lymphocytes of women with PE do not exhibit the same cellular hypo-responsiveness to fetal cells than those of normal pregnant women. This idea is further backed by realizing that the activity of proinflammatory cytokines, such as TNF-α, IL-6, IL-2 and IL-12, are increased in women with PE. The increased activity of these cytokines can in turn result in endothelial dysfunction.

3.1.2 GENETIC FACTORS

Preeclampsia is two to five times more prevalent among mothers, daughters, sisters, and granddaughters than in mothers-in-law, daughters-in-law, or control populations; suggesting the involvement of both maternal and fetal genes in the syndrome. Since both genotypes must be considered, deciphering the genetic involvement in PE becomes challenging. Maternal and fetal genes may have independent or interactive effects on the risk of pre-eclampsia. Other pregnancy complications, such as IUGR and GDM, follow the same challenges. But in general, the role of the placenta in the primary pathogenesis of the
complications of pregnancy, particularly in preeclampsia, strongly suggests a fetal contribution to the susceptibility to these disorders.\textsuperscript{126,127} Previous studies have reported a higher rate of pre-eclampsia in pregnancies fathered by men who were themselves born of pre-eclamptic pregnancies, suggesting the paternal role in the disorder.\textsuperscript{128} According to the genetic conflict hypothesis, fetal (paternal) genes will be selected to increase the transfer of nutrients to the fetus, whereas maternal genes will be selected to limit transfer in excess of a specific maternal optimum.\textsuperscript{10} Fetal genes are predicted to raise maternal blood pressure in order to enhance the uteroplacental blood flow, whereas maternal genes act the opposite way.\textsuperscript{10} Based on this logic, we could interpret the endothelial dysfunction in mothers with preeclampsia, as a fetal attempt to compensate for an inadequate uteroplacental nutrient supply.\textsuperscript{10}

3.1.3 ABNORMAL PLACENTATION

All eutherian species have placenta to deliver nutrition to the fetus. To accomplish this task, the placenta is developed in two stages: 1) invasion of the trophoblast cells into the uterus to promote maternal blood flow to the implantation site, and 2) increasing the surface area of this site by complex folding and branching of the chorionic trophoblast surface for more nutrition to pass through the placenta corridor.\textsuperscript{129} Interference with either one of these developmental events can endanger the life of the fetus and lead to serious pregnancy complications.\textsuperscript{129} In fact, it is widely accepted that abnormal placentation is involved in the genesis of preeclampsia,\textsuperscript{130,131} IUGR\textsuperscript{24} and IUFD.\textsuperscript{129} The very fact that placental delivery reverses the symptoms of preeclampsia,\textsuperscript{132} suggests that the placenta, the placental hormones\textsuperscript{133}, and the placental perfusion have a pivotal role in the condition.\textsuperscript{23,131} Successful placentation is crucial in fetal development and can directly impact perinatal outcome.\textsuperscript{134} Furthermore, laboratory examinations of placenta after delivery have been shown to relate placental pathology to adverse perinatal outcomes.\textsuperscript{135} The adverse perinatal outcomes that has been linked to placental abnormalities include stillbirth,\textsuperscript{136} infant death syndrome,\textsuperscript{137} PIH,\textsuperscript{8,138} GDM,\textsuperscript{138} and asymmetric IUGR,\textsuperscript{139} where the vital organs of a fetus, such as the brain and heart, are protected at the expense of the liver, muscle and fat.
3.1.4 PLACENTAL FACTORS

It has been shown that the sera of PE patients are toxic to endothelial cells.\textsuperscript{140, 141} This toxicity, along with the clinical symptoms of PE, seems to remit after delivery.\textsuperscript{140} Furthermore, the toxicity seems to modulate endothelial cell function rather than damage the cells.\textsuperscript{96} Some studies have suggested that oxidative stress plays a key role in this toxicity.\textsuperscript{96} Activated decidual large granulocytes produce cytokines, proteases and oxygen free radicals.\textsuperscript{96} When oxygen free radicals are not eliminated by antioxidants, lipid peroxide formation is induced,\textsuperscript{142} which can cause endothelial damage.\textsuperscript{143} This is supported by the results of other studies that have reported increased levels of lipid peroxidation products in the blood, decidua basalis,\textsuperscript{144} and also in the placentae of PE subjects,\textsuperscript{142} as well as the studies that have shown administration of high dose of antioxidants can in fact reduce the risk of PE.\textsuperscript{101} The alterations in the lipid concentration in PE could be caused by cytokines, like TNF-\(\alpha\), IL-1 and IL-6.\textsuperscript{145}

3.1.5 ENDOTHELIAL DYSFUNCTION

The endothelium plays a major role in the vascular changes in pregnancy.\textsuperscript{96} In normal pregnancy, the increased presence of vasodilators and/or the decreased production of vasoconstrictors cause vasodilation.\textsuperscript{146} In PE there is overwhelming evidence for functional\textsuperscript{101, 102} and structural\textsuperscript{104} disorder in the endothelium, which are detected in a variety of ways. A marker for endothelial dysfunction that has recently been widely studied is Endothelin-1 (ET-1), a potent vasoconstrictor produced by many tissues including lung, kidney, brain, endocrine glands, and placenta.\textsuperscript{147} ET-1 is also expressed by several cell types, the most prominent source is vascular endothelium. Elevated blood ET-1 levels are associated with a variety of diseases, particularly endothelial dysfunction, which, as we have seen, has been implicated for a number of pregnancy complications.\textsuperscript{147-150} In one study, uterine vein ET-1 levels were three times higher in PE.\textsuperscript{148} Another prominent marker is vascular endothelial growth factor (VEGF), which is not only involved in vascular growth, but also has a vasoactive effect and causes increased vascular permeability.\textsuperscript{151} Circulating levels of VEGF were found to be elevated\textsuperscript{151-154} and correlated to blood pressure in patients with PE.\textsuperscript{155} Increased VEGF concentrations could contribute to the extravasation of plasma proteins and subsequent development of proteinuria, both characteristic features of PE.\textsuperscript{156}
3.1.6 LIFESTYLE FACTORS

It has been long understood that lifestyle habits play an important role in clinical manifestation of pregnancy complications. Women who adopt a sedentary lifestyle, have a poor diet, and are exposed to excess psychological stress are more susceptible to complications during their pregnancies.

3.2 Pathophysiology of Pregnancy Complications

While there are multiple factors involved in the pathophysiology of pregnancy complications considered in this study, it is likely that abnormal placentation plays an important common role. More specifically, it is believed that endothelial dysfunction is the common denominator of the clinical symptoms of many complications of pregnancy, in particular those that are related to hypertension. Placental ischemia is thought to lead to widespread activation/dysfunction of the maternal vascular endothelium that results in enhanced formation of endothelin, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators. Oxidative stress, impaired function of vasodilators, cellular and humoral immunological factors play an important role in the pathophysiology of the placenta.

It is important to understand the relationship between placental dysfunction and oxygen intake. As the normal pregnancy progresses, extravillous trophoblasts surround and invade the arterial walls, fibrinoid matrix accumulates, and musculoelastic tissue is lost. This in turn creates a high-flow, low-resistance zone within the placenta where maximal exchange of nutrients, respiratory gases, and waste products between the maternal and fetal circulations can occur. Any disruption to transfer at any point in the oxygen pathway could translate into absent or reversed end-diastolic flow (A-EDF or R-EDF) velocity in the umbilical arteries, which can be detected on a Doppler velocimetry. Studies have shown that such disruptions cause the small fetuses of IUGR pregnancies to become hypoxic and acidotic. As fetuses become hypoxic, they begin to develop a mixed respiratory and metabolic acidosis. In a study of small fetuses with A-EDF on Doppler velocimetry of the umbilical artery, 88% of the fetuses were either hypoxic, acidotic, or both.

An interesting phenomenon during pregnancy is the presence of hemodilution. In pregnancy, plasma volume increases progressively beginning in the first trimester, peaking in the third
trimester, and maintaining that peak level until delivery.\textsuperscript{164, 165} It is believed that this increase in plasma volume is due to the fetal requirements for higher circulation during its development.\textsuperscript{166} However, while plasma increases by as much as 50%, the red blood cells increase only about 30% during this plasma expansion period, resulting in a physiologic dilution of red blood cells called “hemodilution” that can look a lot like anemia.\textsuperscript{167} In a normal pregnancy, after the 28th week of gestation, the hemoglobin values begin to rise again as the plasma stops expanding and red blood cells continue to increase.\textsuperscript{167} In complicated pregnancies either the expansion of plasma volume is inadequate resulting in “small for gestational age” babies, or the platelet count values don’t increase sufficiently, leading to a condition called thrombocytopenia\textsuperscript{168} as well as other cardiovascular deterioration\textsuperscript{169}.

Aside from platelet count, uric acid also plays an important role in the pathophysiology of pregnancy, particularly in preeclampsia and eclampsia. In pregnancy, maternal serum uric acid level decreases until the 8th week of gestation and remains at this level until the 24th week when it starts increasing until term.\textsuperscript{170} At term, it is higher than the pre-pregnancy level and an elevated concentration is maintained for at least 12 weeks postpartum.\textsuperscript{170} In a normal pregnancy, the renal clearance of uric acid is high, especially in the middle period when the serum level is low in spite of the increased production of uric acid by the fetus.\textsuperscript{171, 172} However, in preeclamptic pregnancy, this renal clearance of uric acid is not maintained, resulting in higher uric acid concentrations (more than 2.0mg\% above normal for gestational age\textsuperscript{169}) than in normal pregnancy.\textsuperscript{169, 171} It has been shown that women with abnormal Doppler have a significantly higher levels of serum uric acid level, a condition called hyperuricemia,\textsuperscript{173} and Hyperuricemia is a well-recognized risk factor for cardiovascular diseases,\textsuperscript{173} and in preeclampsia, the degree of hyperuricaemia has been shown to reflect the severity of the disorder.\textsuperscript{174} It is important to point out that often the fall in the platelet count and rise in the serum uric acid levels coincide.\textsuperscript{174}

3.2.1 PREGNANCY INDUCED HYPERTENSION

Although PIH has been identified as the leading cause of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for its pathogenesis have not yet been clearly understood.\textsuperscript{160} Some studies suggest that the reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles
to be the initiating cause. This insufficient perfusion causes the placenta to secrete various kinds of proinflammatory molecules that damage the maternal endothelial cells, and in consequence, vascular resistance is increased that further burdens maternal organs with hypertension. It is thought that systemic inflammatory response and dysfunction of the maternal endothelial cells represent the pathological scheme of PIH.

3.2.2 PREECLAMPSIA AND ECLAMPSIA

Similar to PIH, it is believed that the symptomatic phase of preeclampsia and eclampsia originates with the placenta, as delivery of the fetus alone is not palliative, and only removal of the entire placenta will cause the condition to remit. Recent research has begun to elucidate the link between placental ischemia and hypertension in the preeclamptic patients. The placental ischemia, in turn, results in hypoxia and leads to the release of soluble factors, in particular angiogenic factors, such as vascular endothelial growth factor (VEGF) and its variant soluble fms-like tyrosine kinase-1 (sFlt-1), into the maternal bloodstream, which act as pathological agents. During pregnancy, VEGF and sFlt-1 are both produced in abundance from the placenta, and one of the recent findings in preeclampsia research has been that sFlt-1 is elevated significantly in response to placental ischemia. In fact, several studies have suggested that inhibition of sFlt-1 can actually attenuate many of the symptoms of preeclampsia in animals. In humans, a small pilot study demonstrated that removal of sFlt-1 could improve BP and proteinuria in patients suffering from early-onset preeclampsia. All this data point to the hypothesis that the release of soluble factors into the maternal blood stream from the ischemic placenta is a key event in the pathogenesis of preeclampsia. In addition to the soluble factors, the maternal immune responses are also induced by placental ischemia, which results in elevated circulating levels of inflammatory cytokines (such as TNF-α and IL-6) and contribute significantly to the maternal symptoms. Finally, as we saw earlier, several studies have suggested that endothelin-1 plays a key role in the pathophysiology of preeclampsia. It is further suggested that high levels of endothelin-1 in preeclamptic women act as a common pathway by which the antiangiogenic factors and autoimmune response lead to maternal hypertension. Accordingly, sFlt-1, placental growth factor, endoglin, and VEGF, all of which increase 4–8 weeks before onset of the disease, may be useful predictors of pre-eclampsia.
The effect of systemic endothelial dysfunction leads to impairment in many organs. This impairment in the hepatic endothelium contributes to onset of the HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count) syndrome, in the cerebral endothelium induces refractory neurological disorders, and in the renal endothelium decreases glomerular filtration causing proteinuria- all of which could eventually lead to eclampsia. Finally, endothelial dysfunction promotes microangiopathic hemolytic anemia, and vascular hyperpermeability associated with low serum albumin which in turn causes edema, particularly in the lower limbs or lungs observed in severe preeclampsia and eclampsia.

3.2.3 GESTATIONAL DIABETES
During normal pregnancy, there is a slight but progressive decrease in insulin sensitivity. To maintain a proper glucose metabolism in pregnancy, the maternal production of insulin must increase to counteract the fall in insulin sensitivity. In women with GDM, this increase in production of insulin does not occur. Hormones present in the pregnancy, especially human placental lactogen, are thought to be responsible for this shortfall. At least one study, has suggested that the reason only a subgroup of women suffer from this hormonal impact may be related to the antigenic load imposed by the fetus itself. The rationale for this hypothesis is that some transplant recipients develop diabetes shortly after the operation with very similar characteristics as GDM. Again, the inability to handle the fetal antigenic load has been suggested to be due to improper development of placenta, which some authors have suggested to be due to excessive oxidative stress.

3.2.4 INTRAUTERINE GROWTH RESTRICTION AND SMALL FOR GESTATIONAL AGE
Similar to preeclampsia, levels of endothelin-1 have been shown to be elevated in pregnancies complicated by IUGR, suggesting a common etiology. This common etiological factor appears to be the reduced trophoblast invasion that leads to deficient conversion of the myometrial segments of uterine spiral arteries. Defective trophoblast invasion will result in reduction of uteroplacental blood flow and in turn less nutrients to the fetus. This has long been implicated in the causation of IUGR, SGA, and preeclampsia.
3.3 Doppler Velocimetry
Doppler assessment is a non-invasive procedure and hence acceptable to patients. It is a reliable method of examining utero-placental perfusion and identifying many conditions that would be harmful to the mother and the baby. World Health Organization has stated that "Diagnostic ultrasound is recognized as a safe, effective, and highly flexible imaging modality capable of providing clinically relevant information about most parts of the body in a rapid and cost-effective fashion" Obstetric ultrasound is primarily used to find out the date the pregnancy, confirm fetal viability, determine location of the fetus and the placenta, check for the number of fetuses, check for any physical abnormalities, assess fetal growth (evidence of IUGR), check for fetal movement and heartbeat, and determine the sex of the baby.

3.3.1 DOPPLER MEASUREMENTS
In a typical pelvic ultrasound study, the following parameters are measured:

a) Fetal measurements
   i) Bi-paredial diameter or the diameter of scull in mm (BPD),
   ii) Head circumference in mm (HC),
   iii) Abdominal circumference in mm (AC),
   iv) Femur length in mm(FL),
   v) Fetal heart rate in bpm (FHR), and

b) Placental data
   i) Position of placenta in relations to the cervix and
   ii) Grading of placental maturity

c) Gestational age - Early ultrasound examination, ideally at eight to 13 weeks of gestation, is also an accurate method for estimating gestational age. In a full Doppler study, the following parameters are measured for left uterine artery, right uterine artery, umbilical artery, and fetal middle cerebral artery:
a) Systolic over diastolic ratio (S/D ratio) - When this number is above 2.6, it is considered elevated. Elevated S/D ratio when accompanied by a diastolic notch can be considered as a marker for PE and IUGR. A diastolic notch is seen as a trough like notch between the systolic and diastolic phases in a flow velocity waveform of an ultrasound and has been shown to be closely associated with uteroplacental insufficiency.

b) Peak systolic velocity (Vmax), which is used to detect fetal anemia; 200

c) Minimum forward diastolic velocity (Vmin), which is the minimum forward diastolic velocity in unidirectional flow or the maximum negative velocity in diastolic flow reversal.

d) Pulsatility Index (PI) in an arterial blood-flow velocity waveform index designed to quantify the pulsatility or oscillations of the waveform. The index is particularly valuable when there is diastolic flow reversal, i.e. bidirectional flow. PI is calculated from values of V_max and V_min in the following formula and the lower values of it shows improvement:

\[
PI = \frac{(V_{\text{max}} - V_{\text{min}})}{(V_{\text{max mean}})}
\]

where \( V_{\text{max mean}} \) is the maximum velocity averaged over (at least) one cardiac cycle

e) Resistance Index (RI) in an arterial blood flow velocity waveform, intended for use in arteries where there is no reverse flow. It should be noted that although increased vascular resistance may increase the RI, the index is also affected by several other factors, such as upstream stenosis, vessel-wall compliance, elevated blood pressure and heart rate. At increasing heart rates, the systolic upstroke occurs earlier on the declining diastolic velocity curve, resulting in an increase in the end-diastolic velocity. The lower the values of RI, the less resistance there is in the arterial blood flow. RI is calculated from the following formula:

\[
RI = \frac{(V_{PS} - V_{ES})}{V_{PS}}
\]

where \( V_{PS} \) is the peak systolic velocity,
and \( V_{ES} \) is the end-diastolic velocity
3.3.2 DOPPLER DURING PREGNANCY

Recent findings indicate that indices of uterine artery resistance correlate not only with birth weight\textsuperscript{201}, but also with the extent of trophoblast invasion.\textsuperscript{197,202,203} This is important because, as we have seen earlier, the placental dysfunction is strongly implicated as a contributor to many complications of pregnancy. As a rule, demonstration of an absent or reversed flow in end diastole in the umbilical arteries carries with it a very specific indication of serious fetal compromise.\textsuperscript{204} In a cross-sectional study of 265 consecutive pregnant women attending routine ultrasound examination at 11-14 weeks' gestation, both uterine arteries were identified using color Doppler ultrasound and the uterine artery resistance index (RI) was measured.\textsuperscript{197} The objective was to determine reference values for first-trimester RI in healthy pregnant women with uncomplicated pregnancies and to investigate the relationship between uterine artery Doppler indices and birth weight. The 5th, 50th and 95th centiles for uterine artery RI between 11 and 14 weeks' gestation were 0.53, 0.71 and 0.85, respectively. The study reported a significant negative correlation between birth weight and first-trimester uterine artery Doppler parameters. In one study, it was shown that pregnant women with abnormal Doppler had significantly higher serum uric acid level and significantly lower platelet count than the group with normal Doppler.\textsuperscript{168} The same study also found that the incidence of IUGR, low Apgar score, perinatal deaths and operative delivery for fetal distress was significantly higher in the group with abnormal Doppler.

3.3.3 DOPPLER AS A PREDICTOR

Accurate prediction of pregnancy complications, in particular pre-eclampsia (PE) and intrauterine growth restriction (IUGR), is crucial to improve maternal and perinatal outcomes.\textsuperscript{205, 206} Doppler Velocimetry has been the most widely used marker for predicting pregnancy complications. There is substantial evidence in the literature that there is a correlation between uterine artery resistance and manifestation of complications, such as PIH,\textsuperscript{207} preeclampsia,\textsuperscript{202, 208-213} SGA,\textsuperscript{201, 213, 214} IUGR,\textsuperscript{202, 207, 214, 215} and preterm deliveries\textsuperscript{207, 216, 217}. However, expert opinions vary on the gestational age to perform the Doppler assessment to obtain the best predictive results. Some suggest a first-trimester uterine artery examination,\textsuperscript{208-210, 212, 214, 216} while others prefer a mid-gestation or third trimester assessment.\textsuperscript{201, 207, 213, 218}
3.4 Effects of Stress on Pregnancy

Emotional and psychological stress has been shown to aggravate chronic pain, promote coronary heart disease, and weaken the immune system\textsuperscript{219}. Stress is a powerful sympathetic nervous system stimulant, leading to increased heart rate and blood pressure.\textsuperscript{220} In the earlier chapters, we saw how lifestyle stress can impact the health and quality of life of the mother. In this chapter we see how this stress can impact the fetus and the outcome of the pregnancy. Psychosocial stress in pregnancy has been defined as “the imbalance that a pregnant woman feels when she cannot cope with demands...which is expressed both behaviorally and physiologically”.\textsuperscript{221} Psychosocial stress during pregnancy (‘maternal stress’) has been shown to adversely affect the pregnancy outcomes.\textsuperscript{222} In fact, several studies have reported that events in the maternal environment will filter through the placental barrier and can affect its development.\textsuperscript{223, 223, 224} Furthermore, there is now a mounting evidence that maternal stress can, not only increase the risk of morbidity and premature mortality,\textsuperscript{225, 226} but it can also predispose the affected individuals to diseases over the course of their lives.\textsuperscript{227} It is then not surprising that the National Institutes of Health (NIH) and the World Health Organization (WHO) have both advised that the role of maternal stress during pregnancy should be given high research priority.\textsuperscript{228, 229} The research that has followed these recommendations have linked maternal stress to an increased risk of specific diseases such as malformations,\textsuperscript{222} asthma,\textsuperscript{230} mental and behavioral disorders,\textsuperscript{231} and attention deficit hyperactivity disorder in the childhood. These results were confirmed by a large population-based cohort study that found maternal life stress during pregnancy was associated with an increased risk of a wide range of diseases during childhood.\textsuperscript{232} Maternal stress has also been shown to increase the rate of spontaneous abortions and preterm birth.\textsuperscript{233}

A strongly supported hypothesis relies on the activity of the hypothalamic-pituitary-adrenal (HPA) axis to explain biologically the effects of maternal stress on the fetus.\textsuperscript{234} Activation of the HPA axis, in response to physical or psychological stress, results in the release of circulating cortisol.\textsuperscript{234} In stressful situations, elevated maternal cortisol could exceed the placental capacity to degrade it, cross the placental barrier and influence the developing brain and/or ‘program’ the fetal HPA axis.\textsuperscript{235} At the same time, maternal stress could cause a constriction of the uterine artery, leading to decreased blood flow to the fetus.\textsuperscript{234} The resulting fetal hypoxia may hinder fetal development and predispose the child to health problems later in life.\textsuperscript{236}

Effects of Yoga in High-Risk Pregnancy - PhD Thesis of Abbas Rakhshani
In connection with psychological stress, oxidative stress in utero–placental tissues also plays a key role in the development of pregnancy complications. Modern lifestyle exposes us to many ‘free radicals’ through pollution, pesticides, and preservatives. Free radicals are organic molecules having some unpaired electrons, which makes them highly reactive and prone to bond with oxygen atoms. The most important free radicals seem to be reactive oxygen species (ROS) and reactive nitrogen species (RNS). Formation of ROS and RNS in the human body can cause oxidative damage to the organ tissues and cells. In normal pregnancies, the production of free radicals and lipoperoxidation increase towards the end of the pregnancy, as compared to non-pregnant women. At the same time, the antioxidant capacity gradually increases during pregnancy, leading to an oxidative balance that is maintained throughout pregnancy. On the other hand, a lack of balance between free radicals and antioxidants leads to oxidative stress. Diet rich in antioxidants, such as vitamin C, vitamin E, carotenoids, and flavonoids, have been suggested to scavenge ROS and RNS.

3.5 Effects of Exercise on Pregnancy

Exercise has been shown to reduce pregnancy related physical problems, such as fatigue, varicosities, and swelling of extremities, as well as psychological disorders such as insomnia, stress, anxiety and depression. Fetuses of exercising women may tolerate labor better than those of non-exercisers. Furthermore, clinical evidence of stress, as exhibited by meconium, fetal heart rate pattern and Apgar scores is less frequent in women who exercise at 50% of preconception level throughout pregnancy, compared with well-conditioned athletes who discontinued exercise before the end of their first trimester. In contrast, a sedentary lifestyle during pregnancy may contribute to loss of muscular and cardiovascular fitness, excessive maternal weight gain, raised risk of gestational diabetes mellitus, and pre-eclampsia.

In a study conducted in Japan, 573 primiparous women underwent simple water exercises. Blood pressure and the incidences of hypertension, proteinuria and leg edema were compared with 264 primiparous women in the control group who did not practice these exercises. Significant reduction in systolic and diastolic blood pressure was reported in the water-exercise group after 20 weeks of water exercises. Furthermore, the incidence of proteinuria...
was reduced by 53%, edema by 60%, and preeclampsia by 57% in the water-exercise group as compared to the control group.

It has been suggested that regular physical activities may protect against preeclampsia by intervening at three key stages\textsuperscript{248} in the disease process:

a) Enhanced placental growth and vascularity (protection against abnormal placental development),

b) Reduction of oxidative stress,

c) Reversal of endothelial dysfunction.

3.6 Effects of Other Mind-Body Therapies on Pregnancy

Mind-body therapies follow the beliefs of many ancient medicine systems that the self is comprised of the mind and body. Therefore, if by “healing” we imply "to make whole," the body cannot truly be healed without healing the mind. The conventional medicine is mainly focused on removing the symptoms of the disease, while traditional mind-body therapies seek to remove the root cause of them. Yet, both systems have their duly earned place in treating ailments. Mind-body therapies usually require a long time to address the root cause of ailments; therefore in emergencies, it is the allopathic medicine that saves lives. In contrast, using pharmacological solutions for a long period of time to manage ailments may not be the best alternative. In general, mind-body therapies incorporate a wide array of modalities, which all center on the connection in healing between the mind and the body. There are many different mind-body therapies. Some of the techniques that have previously been studies during pregnancy and/or are relevant to this study are very briefly discussed bellow.

3.6.1 MEDITATION AND RELAXATION

Although meditation and relaxation have long held a place in religious and spiritual contexts, it wasn't until the late 1960's that they were studied in traditional western medicine.\textsuperscript{250} Meditation and relaxation are best used together for therapeutic purposes.\textsuperscript{219} The effects of meditation were first detailed in a research conducted by Dr. Herbert Benson at Harvard University Medical School who described a state of relaxation induced by meditation, which manifested itself in the form of decreased sympathetic nervous system activity and increased parasympathetic nervous system activity.\textsuperscript{219} While many meditation techniques are based on
concentration on a single object or action, mindfulness meditation technique encourages the practitioner to be in the present and stay fully aware of his/her surroundings. In pregnancy, mindfulness meditation has been used to improve the pregnant woman’s mood, reduce her stress,

3.6.2 ACUPUNCTURE
Acupuncture literally means to puncture with a needle. It originated in China many centuries ago and soon spread to Japan, the Korean peninsula and elsewhere in Asia, where it is widely used in health care systems, officially recognized by governments, and well received by the general public. In the Western countries, its popularity is tempered by skepticism of its true therapeutic effect; some have claimed that it works merely through the placebo effect, the power of suggestion, or the enthusiasm with which patients wish for a cure. According to Traditional Chinese medicine, stimulating these points can correct imbalances in the flow of qi (corresponding to prâṇa in yoga) through channels known as meridians (corresponding to nadhis in yoga), although scientific research has not found any histological or physiological correlates for qi, meridians and acupuncture points. The advantages of acupuncture are that it is simple, convenient, has few contraindications, and is safe if it is performed properly by a well-trained practitioner. Unlike many drugs, it is non-toxic, and adverse reactions are minimal. This is probably one of the chief reasons why acupuncture is so popular in the treatment of chronic pain in many countries. Acupuncture has also been shown to be effective in reducing pain, nausea, and insomnia during pregnancy.

3.6.3 QIGONG
Qigong (pronounced “chee-gong”) means “cultivating vital energy”. It is an over 5000 year-old Chinese health method that combines slow movements with mental awareness and breathing to increase and balance a person’s vital energy (qi). In some texts, it has been referred to as Chinese yoga, due to its similarity to the yoga practices to balance the prâṇa. In pregnancy, Qigong relaxation techniques were shown to reduce the frequency of incidence of PIH.
3.6.4 GUIDED IMAGERY

Interactive Guided Imagery (IGI) and visualization are therapeutic techniques that lead the participant through a series of images that promote relaxation by calming the body's natural anxiety-provoking chemicals. These images are not restricted to visual pictures, but may involve any of the body's other senses, including touch, smell, motion, and hearing. Imagery is a unique field within mind-body therapies because it can be a stand-alone therapy, as well as an important component of other mind-body therapies, as it has been used in this research study. For example the repeating of a mantra in meditation is a type of imagery and the use of imagery is evident in biofeedback and hypnosis. Studies have shown that imagery has profound and dramatic effects on heart rate, respiration, blood pressure, blood lipids, pain perception, and immune function. As of yet, there are no previous studies that has effectively investigated the effects of IGI in pregnancy and therefore, this study the first of its kind in this regard.

3.7 Effects of Yoga During Pregnancy

Yoga is an economical, low-impact, stress-reducing, and non-invasive intervention used in prevention and management of many ailments. Having few side effects and offering much in the way of lifestyle benefits, yoga is safe, it is simple to learn, and can be practiced even by elderly, ill, or disabled individuals. It is important to understand the proposed mechanism that yoga improves the condition of different ailments.

As we saw in chapter 2, lifestyle stress can play a major role in the manifestation of ailments. Yoga is able to rehabilitate the body to its original and natural way of handling stress by introducing continuous stimulations through yoga āsanas, breathing, guided imagery, and visualization techniques, followed by mindful rest. Many studies done by our institution have demonstrated that meditation, breathing, and relaxation techniques have a direct and positive impact on the activities of the autonomic nervous system. In this section, we review the meaning and benefits of yoga, different elements of yoga, the various paths of yoga, and finally the role and effect of yoga in pregnancy.
3.7.1 MEANING OF YOGA

Yoga is derived from the sanskrit root verb ‘yuj’ meaning ‘to unite’. Although many people think this term refers to union between body and mind or body, mind and spirit, the traditional acceptance is union between the Jivatman (living soul) and Paramatman (higher soul) that is between one's individual consciousness and the Universal Consciousness. Therefore Yoga refers to a certain state of consciousness as well as to methods that help one reach that goal or state of union with the divine.

3.7.2 THE 5 POINTS OF YOGA

To clarify the science of Yoga and make it accessible to the majority of seekers, Swami Vishnudevananda extracted its essence and presented it in these universal principles for physical and mental health as well as spiritual growth.

3.7.2.1 PROPER EXERCISE (āsanas)

Our physical body is meant to move and exercise. If our lifestyle does not provide natural motion of muscles and joints, then disease and great discomfort will ensue with time. Yoga āsanas are physical postures often imitating the natural positions of the animals meant to make the mind tranquil. Through these postures, the physical revitalization and deep relaxation and mental calmness are achieved.

3.7.2.2 PROPER BREATHING (PRĀNAYAMA)

Yoga teaches us how to use the lungs to their maximum capacity and how to control the breath. Proper breathing should be deep, slow and rhythmical. This increases vitality and mental clarity.
3.7.2.3 PROPER RELAXATION (SAVĀSANA)

Long before the invention of cars, planes, telephones, computers, freeways and other modern triggers of stress, the Rishis (sages or seers) and Yogis devised very powerful techniques of deep relaxation. In fact, many modern stress-management and relaxation methods borrow heavily from this tradition. By relaxing deeply all the muscles the Yogi can thoroughly rejuvenate the nervous system and attain a deep sense of inner peace.

3.7.2.4 PROPER DIET (VEGETARIAN)

Besides being responsible for the building our physical body, the food we eat profoundly affect our mind. For maximum body-mind efficiency and complete spiritual awareness, Yoga advocates a lacto-vegetarian diet. This is an integral part of the yogic lifestyle.

3.7.2.5 MEDITATION

Meditation is a yogic process of providing deep rest to the system by allowing the mind to calm down to its basal states. Features of meditation are:

- Mind dwell on a single thought of choice.
- Deep relaxation of all part of the body.
  - Reduced metabolic rate.
  - Freshness, lightness and a feeling of expansion at mental level
  - Calmness, peace and serene bliss
  - Continuous awareness

The benefits are many. Improved concentration, memory, emotional equipoise and higher creativity are observed.

3.7.3 THE PATHS OF YOGA

There are four main paths of Yoga - Karma Yoga, Bhakti Yoga, Jnana Yoga and Raja Yoga. Each is suited to a different temperament or approach to life. All the paths lead ultimately to the same destination - to union with Brahman or God - and the lessons of each of them need to be integrated if true wisdom is to be attained.27948
3.7.3.1 KARMA YOGA
Karma yoga is the path of action with an attitude of detachment to the fruits of one’s action. It is the path chosen primarily by those of an outgoing nature. It purifies the heart by teaching how to act selflessly, without concerns for rewards. By detaching from the fruits of one’s actions and making those results an offering to God, ego becomes sublimed. To achieve this, it is helpful to keep the mind focused by repeating a mantra while engaged in any activity.

3.7.3.2 BHAKTI YOGA
This path appeals particularly to those of an emotional nature. The Bhakti Yogi is motivated chiefly by the power of love and sees God as the embodiment of love. Through prayer, worship and ritual he surrenders himself to God, channeling and transmuting his emotions into unconditional love or devotion. Chanting or singing the praises of God forms a substantial part of Bhakti Yoga.

3.7.3.3 JNANA YOGA
Taking the philosophy of Vedanta, the Jnana Yogi uses his mind to inquire into its own nature. We perceive the space inside and outside a glass as different, just as we see ourselves as separate from the universal consciousness (God). Jnana Yoga leads the devotee to experience his unity with God directly by breaking the glass and dissolving the veils of ignorance. Happiness analysis is one such technique elaborated in the Upanishads, in which the aspirant contemplates in the nature of true happiness and eventually concludes that such eternal happiness is only a state of inner silence. Jnana yoga is a difficult path, because a prerequisite to it is selflessness actions and pure devotion to God developed through a strong will and discipline.

3.7.3.4 RAJA YOGA
The yoga of mind culture or psychic control gives a practical and ease approach to reach higher states of consciousness. It is based on the Astanga Yoga of Patanjali’s yoga system. Raja Yoga is also called Ahtanga Yoga referring to the eight limbs leading to absolute mental
control. The chief practice of Raja Yoga is meditation. It also includes all other methods that help one to control body, energy, senses and mind. The eight limbs are:

- **Yamas** (the disciplines)
- **Niyamas** (the injunctions)
- **Asanas** (the posture of the body)
- **Prāṇayama** (the control of prāṇa, the life force)
- **Pratyahara** (restraint of senses from their objects of enjoyment)
- **Dharana** (concentration)
- **Dhyana** (meditation- effortless flow of a single thought)
- **Samadhi** (absorption into super consciousness)

### 3.7.4 MAIN PRINCIPLES OF YOGA

- Love and help all living beings
- Respect for life
- Peace in the world
- Have pure thoughts and positive lifestyle
- To do regular physical, mental and spiritual practices
- Protection of the nature and the environment
- Have pure thoughts and positive lifestyle
- To do regular physical, mental and spiritual practices
- Tolerance for all - nationalities, cultures and religions

### 3.7.5 SAFETY OF YOGA DURING PREGNANCY

Stretching exercises, similar to the interventions used in this study, have been widely recommended in maternity care booklets and nursing textbooks and have been found safe in high-risk pregnancy populations. Although at present there are no recommendations from regulatory organizations regarding the role or safety of yoga during pregnancy, there is...
least one randomized trial that has concluded that: “Yoga by its holistic approach to health appears to be safe in pregnancy and leads to improved outcomes.” In any case, one of the primary objectives of this study is to find the feasibility and safety of yoga interventions in high-risk population.

3.7.6 EFFECTS OF YOGA IN LOW-RISK PREGNANCIES

In a randomized controlled trial, Satyapriya et al studied the effects of yoga interventions on the outcome of pregnancies. While this paper is still under peer review, the results are relevant and notable here. The study randomized 96 low-risk pregnant women into two groups of yoga (n=51) and control (n=45). Primigravidae were excluded from the study. The yoga group received an hour yoga session every alternate day for two months, then an hour twice a week for one month; and finally an hour once a week for a month. The control group received antenatal exercises for the same time. Subjects were recruited in 18 to 20 weeks gestation. The results showed significant improvement in the duration of labor in all three stages (p<0.001 in all three cases). Significantly fewer women in the yoga group in contrast to the control required epidural analgesia (p<0.002), emergency c-section (p<0.005), or preterm delivery (p=0.0323). Furthermore, the yoga interventions in this study were able to significantly reduce the clinical manifestation of PIH and IUGR, as well as improve infant birth weight (p<0.001) and APGAR scores (p<0.001).

In a study conducted in Taiwan, Sun et al. investigated the effects of prenatal yoga on the discomforts of pregnancy. This nonrandomized study assigned 88 healthy pregnant women between 26 to 28 weeks gestation to two groups, yoga (n=45) and control (n=43). The yoga group received 30-minutes yoga classes, three times a week, for 12 to 14 weeks. The results showed significant reduction of discomforts in the yoga group (p=0.01).

Beddoe et al. recently showed that mindfulness-based yoga has a positive and significant impact on the sleep quality of the pregnant women. This study recruited fifteen healthy, nulliparous women pregnant with single fetus who were in their second or third trimesters. The subjects attended a weekly mindfulness meditation and prenatal Hatha yoga classes for 7 weeks. Sleep variables were measured by 72-hourr of continuous wrist actigraphy and the General Sleep Disturbance Scale (GSDS) at baseline (pre-study) and at the end of the 7-
weeks intervention (post-study). The baseline data from subjects recruited in their third trimester were used as control. Subjects who began the intervention in the second trimester had significantly longer sleep time, fewer awakenings, and less perceived sleep disturbance at post-study than at baseline. Those who began during the third trimester had poorer sleep over time in spite of the intervention. Using the same interventions Beddoe et al also studied their effects on the maternal psychological and physical distress. The study consisted of only one group (no control) and evaluated self-report measures of psychological distress (Perceived Stress Scale, PSS, and Pregnancy Psychological Profile, PPP), physical distress (pain was measured using a modified version of the Brief Pain Inventory, BPI); salivary cortisol levels were assessed before the first day of the group intervention (pre-assessment) and immediately after completion of the seven weekly intervention sessions (post-assessment). Subjects were all primi, at least 18-years old, and between 12 and 32 weeks gestation. The seven weeks intervention combined elements of Iyengar yoga and mindfulness-based stress reduction techniques. The investigators reported significant reduction in perceived stress (p=0.05), no significant improvement in the PPP instrument (p=0.10), significant reduction in the trait anxiety (p=0.03), and significant lower BPI scores (p=0.02). The average morning salivary cortisol level increased from baseline (3.2±3.7 nmol/L) to post-intervention (16.1±5.4 nmol/L; t=3.06; p<0.01). The results also showed that women who began the yoga intervention in the second trimester reported less pain than women who began in the third trimester, which is consistent with the previous findings that the earlier yoga is practiced in pregnancy the better results that can be expected.

A similar study to that of Sun et al. was conducted in Thailand, where Chuntharapat et al studied the effects of yoga in reducing labor pain and improving maternal comfort and birth outcomes. In this study, 74 primiparous Thai pregnant women above 18 years of age were randomly assigned to two equal-sized groups of ‘prenatal yoga’ group and ‘usual care’ group. The yoga group received 1-hour yoga classes at the 28th, 30th, 32nd, 34th, 36th, and 37th week of gestation (a total of six classes) and were encouraged to practice at least three times per week at home. The control group received usual care only. Pain and comfort were assessed during the labor using multiple instruments: the visual analogue sensation of pain scale (VASPS), the maternal comfort questionnaire (MCQ), the visual analogue scale to total comfort (VASTC), and the pain behavior observation scale (PBOS). The study concluded that
the experimental group had significantly less pain (VASTC: 29.64±9.31 in yoga group vs. 23.67±9.22 in control, p<0.05; VASPS: 83.48±8.89 versus 88.03±8.05, p<0.05) and had more comfort (MCQ: 156.7±13.43 vs. 150.36±11.70, p<0.05; PBOS: 9.82±1.76 versus 8.52±1.97). The first stage of labor and total labor duration were also significantly less in the experimental group but the APGAR scores were not significantly improved.

In a randomized controlled trial, Satyapriya et al. examined the efficacy of yoga in reducing stress of healthy Indian pregnant women.\textsuperscript{93} 90 pregnant women were randomized into two equal sized group (n=45 for each group) of yoga and control. The yoga group received 1-hour yoga sessions, from 18-20 weeks of pregnancy to term, while the control group received prenatal exercises prescribed by the physician. Perceived stress decreased by 31.57\% in the yoga group and increased by 6.60\% in the control group (P=0.001). In addition, the parasympathetic activity increased in the yoga group significantly (p<0.001). This study also found that yoga is effective in improving the quality of life of pregnant women and in enhancing certain aspects of their interpersonal relationships.\textsuperscript{54}

Narendran et al. conducted a study of 335 healthy pregnant women in India that investigated the effects of yoga on pregnancy outcomes.\textsuperscript{55} Subjects recruited between 18 and 20 weeks of pregnancy were assigned to two groups, yoga (n=169) and control (n=166). They were matched for age, parity, body weight, and Doppler velocimetry scores of umbilical and uterine arteries. The yoga group practiced a combination of physical postures, breathing, and meditation for one hour daily, from the date of entry into the study until delivery. The control group walked 30-minutes twice a day during the same period. The study reported that infants in the yoga group had significantly higher weight (p<0.01; 2.78±0.52 kg compared with controls 2.55±0.52 kg) and mothers in the yoga group experienced significantly less complications like intrauterine growth restrictions (p<0.003), pregnancy induced hypertension (p<0.025), and preterm labor (p<0.0006). The reduction in frequency of pregnancy complications was also significant even among the subject with abnormal Doppler study.\textsuperscript{56}
3.7.7 EFFECTS OF YOGA IN HIGH-RISK PREGNANCIES

The present study is the first randomized controlled trial that has used yoga intervention in high-risk pregnancies. However, there have been previous studies that have shown the relationship with pregnancy complications and autonomic systems. One study has shown that preeclampsia is associated with abnormal autonomic behavior and is manifested as increased sympathetic outflow. The results of this study indicated that in the preeclamptic subjects the sympathetic-nerve activity is more than three times as high as that in the normotensive pregnant women and more than twice as high as in the group of non-pregnant women with hypertension. The study concluded that the autonomic nervous system adaptations that promote reduced peripheral vascular resistance in normal pregnancy are absent in preeclampsia.