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REVIEW ARTICLE

New Pharmacologic Therapy for Hypertension in Pregnancy

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Abstract

This project is a thorough exploration of the biochemical and molecular signaling involved in preeclampsia and hypertension in pregnancy. It includes a detailed and documented review of the literature which is used to develop insight into future potential pharmacologic treatments for this complex disorder.

There has been virtually no change for three decades in the treatment of hypertension in pregnancy and it's many namesakes: Pre-eclampsia, gestational hypertension, superimposed preeclampsia, gestosis, etc. all of which shall be referred to in the rest of this article as PIH. In part this is because of an incomplete understanding of its physiology and pathophysiology, partly because the only widely accepted treatment, labetalol, does not work well and causes fetal growth restriction. This is a short review of what we know about PIH and normal placental physiology, what we surmise about the disease process and possible future pharmacologic interventions based on this knowledge, as well as new methods of determining fetal in utero health.

Where We Are (Pathophysiology)

There are clinically determinable risk factors that increase the risk of a particular patient developing PIH. Old or young maternal age, nulliparity, a history of high blood pressure, obesity, first degree relative(s) who developed PIH, family history of early heart disease, histories of diabetes or insulin resistance, kidney disease, lupus, rheumatoid arthritis, thyroid disease, African descent and multiple gestation. All of these except multiple gestation are also known risk factors for later development of heart disease. The only major missing risk factor for heart disease is smoking which actually reduces the risk of developing PIH [1].

Development of PIH does not require the presence of a fetus [2]. One of the usual presenting signs of hydatidiform mole is PIH, usually before the 20 weeks of pregnancy described to satisfy the usual definition of PIH. It must require the presence of at least partially intact placental villi. Patients who have choriocarcinoma in which there are both syncytiotrophoblasts and cytotrophoblasts but not placental villi, do not develop PIH even with advanced disease [3]. It seems logical that, since the presence of at least partially intact placental villi is required for PIH, there must be some communication between cytotrophoblasts and syncytiotrophoblasts as well as possibly fibroblasts in villi, and that the development of hypoxia in one or more layers leads to the development of clinical PIH. It may be however that there is simply not enough tissue volume or endothelial surface area in choriocarcinoma generating enough signals to produce PIH even in patients with advanced disease.

Hypertension develops during pregnancy in several situations which may help elucidate a causation and may help us to treat patients before the final pathophysiologic pathway(s) have been elucidated. Patients with endothelial dysfunction such as lupus especially with active disease and antiphospholipid syndromes also have a predilection for later PIH [4,5]. Patients with endothelial dysfunction not involving excessive clotting such as von Willebrands disease do not have a predilection for developing PIH [6,7]. Hypercoaguability, by itself, apparently does not seem to predispose to PIH [8,9]. So the endothelial dysfunction or, more appropriately overactivity, which has been documented in both lupus and antiphospholipid syndrome is probably the cause of predilection to PIH. Patients with a placental infection such as syphilis or malaria also have an increased PIH incidence [10,11]. This may be from relative hypoxia or misdirected placental signals or increased inflammation in the presence of placental infection. Increased placen-

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tal mass i.e. diabetes, multiple pregnancy, but not from all causes such as large for gestational age fetuses also have an increased frequency of PIH [12-14].

Some pregnancies with small placentas such as from growth restriction also have an increased incidence of PIH and so fetuses with some trisomies or who have a placenta with abnormal chromosomes have a predilection for causing hypertension in their mothers during pregnancy and some do not [15,16]. Another cause of a small placenta leads to a marked decrease in the risk for preeclampsia. This is smoking. It has been noted and well documented that although smoking: Is a risk factor for IUGR, causes a decrease in placental size, and is one of the most prominent risk factors for later heart disease; it does not increase and in fact decreases the risk of PIH developing [17]. Finally sickle cell anemia and iron deficient anemia do not increase the risk of developing PIH although there is obviously less oxygen delivery per volume of blood delivered to the placental bed in both cases [18,19]. Residing above 3300 meters increases the risk of PIH [20].

There are purported pathology changes seen in placentas very early in pregnancy, long before the clinical development of PIH and they are not reversible at the present time. This leads to a placenta with less surface area and therefore less ability to extract oxygen and to a lesser extent, nutrients [21].

There has been a remarkable increase of our knowledge in the basic physiology of placenta growth and interaction between maternal and fetal tissues in early pregnancy [22]. In the first trimester fetal cells block or at least reduce blood flow into the fetal maternal combined vascular space. This blockade is then released. There is a large body of knowledge about growth factors produced in all pregnancies. It is possible that pregnancies destined to become hypertensive have an abnormal pattern of growth factors leading to abnormal placental growth and that abnormal growth later causes an abnormal secretion of vascular factors [23]. There are too many great investigators and investigations to mention in one article. For a good review of the latest information about the placenta and its growth and circulation I would refer you to several monographs, the latest published in 2010 [24-26].

A simplified (very) description of the present state of knowledge of differences in growth factors of early pregnancy between normal and PIH pregnancies is as follows [27]. There are differences in placentas from women destined to develop PIH and normal ones. One of the important growth factors for placental vessels is vascular endothelial growth factor, VEGF [28]. In PIH there is an increased level of soluble fms-like tyrosine kinase [29]. Soluble levels of this protein keep VEGF from activating membrane bound receptors for it which diminishes blood vessel growth [30,31]. Transforming growth factor betas (1-to at least 3) are also important in vessels invading the decidual bed [32,33]. Endoglin is a membrane bound protein that helps in TGFs interacting with cells [34]. Soluble endoglin apparently binds to circulating TGFs again reducing interaction with the membrane bound receptors leading to reduced vessel growth and invasion [35]. Increased levels of soluble endoglin are a risk factor for developing PIH [36]. Bone morphogenetic protein BMP, is another signaling protein with actions similar to TGF [37]. It is also bound and rendered ineffective by binding to soluble endoglin. Both of these soluble receptors sFlt and soluble endoglin are increased early in PIH patients leading to less blood vessels and less invasion in the decidua. PlGf a close homologue of VEGF is produced by the placenta, has similar purported actions as VEGF, and is similarly bound to s Flt s and interacts with VEGF receptors in a similar fashion as VEGF. There is an enzyme produced in the heart and the decidua called Corin that activates both atrial natriuretic peptide (ANP) and its close homologue brain natriuretic peptide (BNP) [38]. It has been found that in preeclampsia there is less activity of this enzyme leading to reduced activation of ANP receptors which are membrane bound producers of cyclic GMP [39]. This in the face of significant elevations of ANP and BNP in symptomatic patients [40]. There have been variants of Corin found in patients with African descendancy that have less trypsin-like enzymatic activity and which leads to less active ANP and BNP activity and hypertension later in life [41]. It has also been found that genetic mutations leading to a less active Corin also lead to preeclampsia [42].

All of these changes affect the growth and development of the placenta in the same way and are all probably at least additive if not multiplicative. So in summary in pregnancies destined to develop PIH the early signaling leading to invasion and vascular and probably cotyledon growth are all diminished leading to a lower maximum blood flow into the decidual bed and a diminished maximum placental absorptive surface area. How this leads to PIH in some but not all pregnancies is unknown at present.

There are probably many more signaling proteins and systems that are deranged in PIH. I have brought these up specifically because they are well documented, have widespread agreement and provide insight into the early developmental abnormalities in PIH and lend credence to another pathophysiology that has many parallels if it is not exactly the same process as occurs in PIH and which already has many experimental pharmacotherapies that disease process is pulmonary hypertension.

After the initial developmental abnormalities of reduced invasion and reduced cotyledon surface area at least in part caused by the previously mentioned signal aberrations there are features which distinguish PIH from normal pregnancy. There are uterine impedance

differences seen very early in gestation by ultrasound that markedly increase a patient's risk of developing preeclampsia later [43]. This is more predictive of severe growth restriction and severe preeclampsia requiring delivery than of later onset of PIH. In the mid-trimester Doppler scanning of the uterine arteries is still predictive of more severe disease but is a better predictor of preeclampsia without growth restriction [44]. In both cases Doppler did not diagnose later disease in patients but simply an increased risk, maybe a markedly increased risk, over the background.

We know that in normal and hypertensive pregnancies the placenta gradually controls the maternal circulation through excretion of all renin system proteins, endothelins, prostaglandins, endoglins, mineralcorticoids,and numerous other peptides and non-peptidal signals [45,46]. We know that all these are produced in both normal and abnormal pregnancies. Some are on average higher in pregnancies destined to develop PIH for example; soluble endoglin and uric acid others are decreased in those pregnancies; such as prostacyclin and nitrous oxide (NO). We can now discuss some of the derangements in signaling systems that occur in clinically apparent PIH. Those described have less to do with vascular growth and more to do with vascular signaling and control. There are increased levels of endothelin in PIH [47]. There is an increased circulating level of ANP in PIH [48]. The interaction of ANP with the ANP receptor family requires the removal of the distant N terminal in the circulating bloodstream. In studies to date whether the circulating level is cleaved active ANP or preANP is unknown. Serum BNP is also increased in PIH [49]. NO production is more uncertain in PIH. In some models nitric oxide metabolites are decreased [50]. There are other models that show an increase or no change in NO activity [51]. Models that lack NO synthase genetically sometimes develop a PIH like syndrome but sometimes do not [52]. However total serum nitrate levels, an indirect measure of NO production, is increased in PIH [53]. This may in part be because we do not know if the NO is coming from the placental bed or the system wide vascular epithelium which has a greater surface area. Probably in clinically apparent PIH there is a greater NO production as a response to the development of PIH. A less controversial change is the increased activity of the Rho-kinase system in PIH. Rho-kinase is an important smooth muscle intracellular signaling pathway involved in vascular tone. Increased Rho-kinase activity leads to increased contraction of myosin-actin and vessel constriction. There is increased expression of Rho-kinase mRNA in human umbilical artery in PIH [54]. The Rho signaling pathway is reduced in normal human pregnancies and increased in clinically diagnosed PIH [55]. This is supported by multiple animal models of PIH [56]. There are undoubtedly other signaling differences between normal and PIH pregnancies but these are mentioned because they show a close parallel with another human vascular abnormality that may be close to identical in signaling abnormalities and these signaling pathways are all amenable to presently available pharmacotherapies.

So to review; pregnancies destined to develop PIH probably produce different ratios of growth factors early in pregnancy which leads to a probably smaller placenta with a smaller surface area compared to the fetus's unique growth potential which we cannot measure. Remember, however that not all small placentas lead to PIH. Some growth restricted fetuses such as trisomy 18, smoking and unexplained early growth restriction are not associated with PIH [57,58]. Chronic anemia does not lead to PIH but acute anemia such as is associated with acute malarial attacks or acute hemolysis do.

Every day in a normal pregnancy the fetus is bigger and therefore needs to have a larger blood volume to support its increasing cardiac output and carcass size. It needs more oxygen and other nutrients just to maintain its status quo. With this a given, a working hypothesis for developing PIH is; a fetus who outgrows it's placental oxygen or other nutrient supply sometimes because of a small placenta i.e. deficient early growth factors, sometimes because of too large a fetal mass i.e. triplets, causing it's placenta to produce a different set of signals after mid-pregnancy into the maternal and possibly the fetal circulation causing maternal development at some tipping point of some or all of the spectrum of PIH and perhaps earlier a change in fetal vascular resistance. Each mother has a unique endothelial sensitivity and a unique production of and response to the same signals that control their circulation and a unique maximum cardiac output and maximum lung oxygen exchange. Each fetus at any point in pregnancy also has a unique sensitivity to vascular signals and a unique growth potential. That is why PIH is so complex a clinical syndrome. In most human disease processes there are multiple genes that contribute to development or lack thereof of a disease. In PIH there are 2 genetic complements that interact in very complex ways to sometimes cause PIH. Discussing the risk of PIH in families brings up the question of whether it is genes on the maternal side or genes on the fetal side or probably more likely, genes on one side interacting with genes on the other side to produce a clinical syndrome form unknown pathological processes.

Why are some known causes of a small placenta i.e. smoking and some trisomies cause a decrease or at least no increase in PIH risk. One explanation is that they both reduce the growth of the fetus as well as the placenta and therefore they do not cause a relative imbalance between placental and fetal growth potential or fetal growth potential and placental transfer potential. It has also been shown that high elevation causes an increase in PIH [59]. My explanation for why high living altitude increases PIH but chronic anemia does not even though

both reduce maximum placental oxygen transport will be discussed later.

So each fetus has a unique requirement for nutrient transfer across the placenta and a unique reaction to a reduction in nutrients, producing a unique amount of differing vascular signals and mother has a unique tipping point at which increasing blood pressure signals no longer lead to increased fetal oxygen delivery and also increasing blood pressure leads to vascular endothelial shear stress causing the eventual development of PIH. How do we overcome this problem and increase the fetal uptake of oxygen and other nutrients at least for a few weeks longer? Drugs that reduce shear stress toxins like ET-1 blockers might allow more placental flow without endothelial stress. If hypoxia is the problem, increasing the maternal oxygen level by supplementation doesn't help because maternal hemoglobin is basically saturated already. The immediate limiting factor is placental surface area and blood flow. Increasing fetal oxygen delivery has to depend on improving the fetal side of placental bed circulation, after maximizing maternal cardiac output. It might be possible to improve fetal oxygen uptake if there is some maldistribution of fetal blood flow to the placenta or widespread reversible arteriospasm of placental supply vessels. There are some hints that some drugs that lower blood pressure also can lead to increased placental growth.

It has also been discovered that local production of nitrous oxide (NO) is involved in maintenance of local blood flow in the placental bed [60]. Increasing local production of NO might be an avenue of manipulation to improve fetal oxygen levels. It has also been determined that local production of prostacyclin is also required for normal fetal decidual circulation [61]. Progesterone is not the method to use since it reduces placental prostacyclin production [62]. This has been known for a long time but recently novel prostacyclin agonists have been introduced which might be an avenue of successful manipulation of placental circulation to enhance fetal oxygen absorption. It has also been determined that at least some of the prostacyclin effect is from G receptor local production of cyclic AMP [63]. We know that healthy pregnancies produce a different levels of nitrous oxide, prostacyclin, renin, angiotensin, aldosterone, and (RAS) metabolites [64-66].

Getting baseline levels of some of these metabolites from blood, urine or even pulmonary outflow (NO) and following some or all of these in individual patients after or even when considering therapy for hypertension, even using ultrasound to use the cross sectional area and average blood velocity of the umbilical vein and dividing this by the estimated fetal weight times the cross sectional area of the abdomen made the same day serially to determine if blood flow per kilogram in the fetus changes positively or negatively with treatment or observation may lead to ways to more acutely monitor how and how much PIH affects fetuses and allow better evaluation of new and old pharmacotherapies.

A New Model for Treating PIH

There are at present no animal models for PIH which completely parallel the disease process in humans. Since they have similar functions i.e. the maximum absorption of oxygen, the best model for fetal placental oxygen transport may be the pulmonary artery system. It has been recently proven that there are oxygen sensing potassium channels in the pulmonary circulation [67,68]. The exact mechanism that causes arterial constriction in the pulmonary arteries as opposed to the vasodilation that occurs in all other systemic arteries exposed to hypoxia has not been completely worked out but involves potassium channel(s) being blocked leading to depolarization of the cell membrane and an increase in calcium ion flux across the cell membrane and release from the sarcoplasmic reticulum leading to smooth muscle activation and vessel constriction. A similar or the same system has recently been described in human placental arteries [69]. The K^{+} channels and of course Ca^{++} release might both be amenable to altered function by pharmacologic intervention.

There has been great progress in understanding pulmonary hypertension (PAH) in the last decade. There are multiple animal models that are now being used to test treatments. There are also multiple trials of new classes of medications treating this disease. This paper supposes that the initial pathophysiology as well as the changes amenable to pharmacological manipulation are the same in PIH and PAH. First, logic tells us that the endpoints of lung and placental physiology are the same, maximized of gas exchange. These organs must have the same or very similar responses to local hypoxia, a diminution in blood flow to low oxygen areas to maximize blood flow to oxygen rich areas thereby maximizing oxygen uptake at any particular cardiac output.

First a brief description of some of the animal models of PAH. All the models rely on at least two stages of stress to induce pulmonary hypertension. In one model injection of a pulmonary vascular irritant, monocratline, a toxic plant alkaloid that causes pulmonary endothelial inflammation or bleomycin the cancer drug known to cause pulmonary toxicity. The rats are then exposed to a hypoxic environment and most quickly develop PAH and die if untreated of cardiac failure within a few weeks [70]. Another model involves removal of one lung and then treatment with SU 4516 a blocker of VEGF and then placement in a hypoxic environment [71,72]. The most interesting model was treatment with SU 4516 in rats that genetically are deficient in T2 cells [73]. In this model SU 4516 alone was sufficient to cause PIH over time, hypoxia was not necessary. This is the first real evidence that maybe our immune system has some participation in developing PIH. In this model rats did

not develop disease if their T cells were reconstituted [74]. B cell depletion in the same model prevented the development of PAH [75]. These animal models of pulmonary hypertension allow measurement of signals before, during, and after disease development and allow the use of experimental treatments based on the signaling abnormalities. There are several pathways that have become abnormal in these models [76]. There is an enhanced production of Endothelin in these lungs before the development and higher levels after the development of PAH [77]. There is an abnormal activation of the RhoA /Rho-kinase system [78]. This system is known to be normally down-regulated in normal pregnancy in rats. It is not known but presumedto be down-regulated in normal human pregnancy [56]. There is a disruption of, bone-morphogenetic-protein, BMP/TGFb signaling in the rat models of PAH especially with the monocratline models [79]. Thromboxane levels are increased [80,81]. Prostacyclin levels are decreased in these models [82]. Nitric oxide levels are decreased in these animal models of PAH and elevated levels of NO from transgenic experiments prevent most models of PAH from occurring [83,84]. Increased levels of cyclic GMP esterase is noted [85]. The RAAS system is also overactive in pulmonary hypertension [86,87]. Thromboxane is implicated in the development of PAH in animal models [88]. In this model inhibiting its synthesis reduces developed pulmonary hypertension. Thromboxane A2 receptors seem to mediate a large part of the arterial pressure elevation in pulmonary hypertension [89]. Prostacyclin therapy is efficacious in both animal models of PAH and in humans [90]. Transforming growth factor beta blockade, from antibodies or a receptor blocker, ameliorated or prevented PAH in a rat model [91]. Mutations in the TGF-beta pathway leading to decreased effect also are associated with reduced PAH in childhood [92]. Elevated TGF-beta levels are associated with PIH in humans [93]. Human mutations with more active TGF-B in small studies are associated with an increased risk of developing PIH [94]. Increased TGF-b is also involved in yet another model of PAH, blockade of it's signaling pathway blocks development of PAH [95]. In closely related signaling, bone morphogenetic protein, (BMP) is also elevated in animal models of PAH and blockade of its signal reduces PAH [37,96]. As was previously mentioned Endothelin is involved in PAH in humans and receptor blockade improves PAH in both animal models and human experience [97]. Genetic disruption of ANP leads to development of PAH in mice models, even without hypoxia [98]. Genetic manipulation to cause excess production of BNP prevents PAH from developing in an animal modes [99]. After PAH develops in animal models increased ANP is secreted probably by the heart in response to the cardiac stress of PAH and the hypoxia used to cause the condition experimentally [100]. In an animal model of neonatal pulmonary hypertension there are increases in cGMP phosphodiesterase which would reduce cytosolic cGMP [85]. In another parallel to PIH there is dysregulated RAAS system in human PAH as it is in PIH [101,102]. Finally uric acid metabolism is also disrupted in PAH as it is in PIH leading to increased uric acid levels [103]. It is unknown if elevated uric acid levels are part of the pathology of PAH or just a marker as it is in sickle cell disease [104]. Some pulmonologists are asking if allopurinol might be beneficial in PAH [105,106].

There are probably more corollaries found between models of PAH and PIH. There is enough to be convinced that at least the early pathophysiology and signaling alterations causing them are of a similar if not an exact match. The various markers seen in these animal models and in human PAH compare in a parallel fashion to the same markers in PIH. It follows that if the same signaling systems respond in a parallel fashion that pharmacological manipulation of these same systems could result in similar improvements in functional disease. Next are several simplified important signaling pathways that are important in the development of PIH and PAH, in both cases affecting the tone of vascular smooth muscle cells.

Supplementary File

Schematic 1: Rhokinase signaling pathway vascular smooth muscle constriction.

Schematic 2: Cyclic GMP signaling pathway vascular smooth muscle relaxation.

A Combined PIH Model (The BYRNE Hypothesis)

If the advances in understanding of pulmonary hypertension are added to what is known about preeclampsia we can better understand both. We have to think about PIH and its treatment in the context of the fetus, the placenta (perhaps decidua), and the mother. The first question to address is why changes in response to hypoxia are adaptive for the fetus. As in the lung, if there are localized areas of relative hypoxia, secretion of local vasoconstrictors on the placental side of the decidua will lead to shunting of blood away from hypoxic areas to better oxygenated areas leading (at the same fetal cardiac output) to enhanced net oxygen uptake. This is adaptive. Increased blood pressure on the fetal side of the circulation also leads to a higher placental flow, and again, an increased net oxygen transport. This is adaptive. On the maternal side increased blood pressure, in response to secreted fetal signals, leads to increased decidual flow since this is dependent on average blood pressure. So in the first phase all these are adaptive for the fetus. When do they become maladaptive? At some tipping point, which has to be different for every fetus, on the fetal side, increasing resistance has to lead to a maximum in cardiac output and so after this increasing resistance leads to decreased placental flow and eventually reduced cardiac blood flow and reduced net oxygen delivery and increased fetal oxygen expen-

diture from increased net cardiac work. In neonatal pulmonary models of PAH increased blood flow in the face of increased resistance leads to vascular smooth muscle hypertrophy and increasing resistance. This has not been looked at in placental vasculature. At some blood velocity point increased pressure is associated with increased shear forces which leads to endothelial resistance and dysfunction. Each day the fetus is bigger and needs more oxygen to continue to grow and for want of a better word, prosper. So adaptations that are helpful today will not be down the road because they have advanced the fetus prematurely along a starling like curve. So a larger fetus requiring increased oxygen delivery will later be unable to effect increasing placental flow.

On the maternal side again increased average blood pressure and perhaps some extra shunting of blood to the decidual bed from other maternal beds, (renal, hepatic?), from vasoconstrictors produced in response to local decidual relative hypoxia lead to increased decidual blood flow and increased net oxygen delivery to the fetus. At some point, which again is different in every mother due to differing sensitivities to vascular signals, different maximum cardiac output, net cardiac reserve, basal metabolic reserve, vascular disease and undoubtedly other known or undiscovered factors, increased blood pressure and vascular shunting does not increase cardiac output and does not increase decidual net oxygen delivery but increases maternal cardiac work and oxygen usage. At some point, also different for each mother, depending on endothelial genetic differences, differences in inflammation baselines and differing levels of endothelial baseline activity, increasing blood pressure leads to shear stress in the maternal endothelium leading to worsening systemic and decidual blood flow and organ dysfunction. There is no direct proof of this hypothesis but it fits with known vascular flow physiology and explains some of the historical risk factors risk for PIH. Anything leading to greater increased potential for fetal but not placental growth, anything reducing placental oxygen transport and size but not fetal growth potential, anything which limits decidual blood flow but not fetal growth potential all increase the appearance of what we call PIH. Limitations in maternal cardiac output, prepregnancy organ or vascular dysfunction, anything that increases baseline inflammation and endothelial dysfunction all increase the appearance of PIH symptoms at an earlier time. Even the most normal pregnant women with sextuplets will develop PIH, while someone with severe dysfunction (say a renal clearance of 25 mls prior to pregnancy or very active lupus) will almost always also develop PIH, even with a small fetal mass. Late in clinical disease there is no drug that will help. The feedback pathophysiology, especially of endothelial dysfunction is not stoppable except by delivery. Even in early in PIH treatment only delays delivery because the very act of helping allows more fetal growth and a higher fetal carcass oxygen requirement down the road. We have to test therapies early in the disease process and these can work in only two ways. First maternal blood pressure has to be lowered to a safe level and maternal cardiac output has to be maximized. Therapies that stop or slow or reverse the endothelial dysfunction will help on the maternal side and may even help on the fetal side. The biggest unutilized therapeutic target is fetal placental resistance. If the PAH model is close to placental flow model in PIH there are multiple novel drug therapies that are effective in PAH. Our goal is not a cure. There cannot be one if this model of PIH is correct. We can only temporarily alter the starling like curve before more fetal growth increases the needed placental flow to transport increasing oxygen demands. Unlike patients in heart failure or pulmonary hypertension,we aren't after permanent treatment. Imagine improvements in neonatal outcome if every PIH patient delivered 4 weeks later with 3 or 4 weeks of intervening growth. Prolonging pregnancy and producing even a 2 week interval of growth would be monumental.

The apparent conundrum of high elevation leading to increased PIH and chronic iron deficient anemia leading to no increase in it. Although they superficially have a common apparent link there is a vast difference in their pathophysiology. The patient at elevation has a shifted hemoglobin oxygen dissociation curve which would tend to reduce fetal oxygen transport. They have expanded extracellular volume before pregnancy leading to a decreased volume reserve capacity later in pregnancy. At elevation because of the decreased alveolar pO_2 level there is an increased tone of pulmonary resistance vessels even at rest and this means that there is increased maternal cardiac work at any cardiac volume output so the maximum increased capacity in cardiac output is less than at sea level. Finally, at elevation, there is a compensatory increase in red cell mass leading to an increased blood viscosity and this must reduce the maximum decidual bed blood flow per minute from the increased resistance to flow and reduces the velocity at which shear forces start to inflame the vascular endothelium. All these are opposite changes from the patient with chronic iron deficient anemia. Their hemoglobin oxygen dissociation curves are shifted towards peripheral (and fetal) oxygen delivery. They are known to have an exaggerated vascular volume increase which allows a greater cardiac output and because of a lower viscosity there is less resistance to blood flow in the pulmonic and decidual beds allowing greater flow at any particular pressure. The low viscosity means there has to be a greater blood velocity before shear stress is initiated in vascular endothelium. For all these reasons it makes perfect sense that PIH is less common in patients with chronic anemia compared to patients living at high elevation. That is the thinking you have to evolve about each patient because they each develop PIH for their own peculiar reasons and they respond to treatment in their own individual way.

Where We Should Go

There may be novel therapies developed when we understand more of the basic physiology of how placentas invade mothers and how they develop more and new surface cotyledons and control maternal blood pressure but these are probably at least a generation away from us. We have to try to develop therapies for clinical patients we have today with the drugs we have available today and with our present limited understanding of PIH. We need to find other agents to add to the drugs in use which will help with the pathologic process occurring in pregnancies. Our therapeutic goal should be the same as it has always been; maintenance of blood pressure below 145 systolic and 95 diastolic. A new goal should be; maximization of uterine flow, umbilical blood flow and fetal growth. If pulmonary hypertension is the closest human model to preeclampsia, drugs that have proven effective for PAH and that are thought safe in pregnancy might theoretically be effective in PIH and should be added in experimental clinical trials to determine if they can reduce fetal stress enough to allow a period of continued fetal growth before delivery.

Where To Go from Here

Calcium channel blockers

These should now represent our first line of treatment for hypertension in pregnancy and maybe experimentally in treating patients at high risk for developing PIH. There is plenty of experimental evidence in animal models and humans that Ca^{++} influx leads to vessel constriction and hypertrophy and that pre-treatment with L-type calcium channel blockers leads to prevention of hypertension in both the pulmonary and systemic circuits. They also work on the fetal vasculature in a similar manner [107-109]. These agents reduce fetal placental resistance and so increase maximum fetal placental flow not minimize it as traditional beta-blockers must. There are experiments showing nifedipine reduces the inflammation associated with preeclamptic placental explants on endothelial cells [110]. Another avenue that this class of drugs might help in more ways than lowering blood pressure.

Nitrates

The second class of drugs we should use are nitrates. The simplest and probably safest is increasing oral intake of arginine which will increase potential NO production by NO synthase [111]. This has already been used in trials for PIH prevention with some small success [112,113]. Direct donors that do not require NO synthase but which by their very nature do not localize NO production to the placental bed are also available and have been used in experimental trials [114]. Nitroglycerin paste and patches can be used. They have longer ranges of activity and lower side effects than sublingual forms. There are many other direct nitrate donors but none with a longer safety record in pregnancy than nitroglycerin [115]. There are some trials of nitrate donor usage in pregnancy with an immediate reduction of umbilical artery pulsatility [60]. This leads some credence to the theory that fetal placental vasoconstriction is present and is reversible to some degree, which would presumably improve fetal oxygen uptake.

Phosphodiesterase 5 specific inhibitors

This class was first used experimentally to replace nitrates in angina. They were found no more effective that nitrates but a relatively common side-effect spontaneous erections occurred. Thus a new class of drug therapy was discovered. This class of drugs is now proven to reduce blood pressure in patients with PAH [116]. There are presently 8 members of this class of drug all work in essentially the same manner preventing the breakdown of cyclic GMP into GMP [117]. This as you are aware from schematic 2 is the downstream step after diffusion of NO into vascular smooth muscle from overlying endothelium. Because PDE5s appear in only some vascular beds these drugs will have more specificity than nitrates but they have a shorter history of clinical usage. They are also reported to increase local NO production so they work in 2 stages of this signaling cascade [118]. Tadafil has the longest effective action and seems to have the fewest side effects. 65 all drugs in this class are pregnancy class B. The only member of this class that should probably be avoided if possible is sildenafil which also blocks PDE6 which can cause visual perception changes and perhaps effects on developing fetal eyes. This class's efficacy in PAH is unquestioned [119].

Endothelin receptor blockers

The next class of drugs that might be beneficial in PIH are endothelin receptor blockers. There are 3 members of this class presently available: Sitaxentan, atrasentan, ambrisentan. Multiple others are not as far along toward clinical usage. They are endothelin-A blockers [120]. No endothelin B blockers are in clinical usage at present. High levels of endothelin have been reported in pregnancy since 1991 and recently have been further implicated in the pathophysiology of preeclampsia [121]. Thus this class of drugs may alleviate some of the end stage maladaptations in PIH and might improve decidual bed blood oxygen transport through local reduction in vasoconstriction. If there is overactive fetal vasoconstriction this might also reduce placental impedance and thus increase net fetal oxygen uptake. Sitaxentan has been withdrawn from the worldwide formulary due to two reported fatal hepatic dysfunction reports. Others in this class such as atrasentan have been prescribed for more than a decade and are apparently well tolerated [122,123]. Atrasentan has been reported to reduce albuminuria in hypertensive type 2 diabetics and so may

reduce the renal effects of PIH at least in the mother [124]. The danger of this of course is that it might not reverse the underlying dysequilibrium in PIH but may take away one of our few well appreciated signs, albuminuria. Two of this class are presently rated X by the FDA to limit usage to clinical studies which is what this whole article is about.

Prostacyclin agonists

There are four prostacyclin receptor agonists in clinical usage at present. Beraprost and iloprost are the two in longest clinical use in PAH. They all stimulate G class seven transmembrane receptors, GCPRs. These drugs are used for treatment of pulmonary hypertension [125]. They might theoretically help placental dysfunction as prostacyclin levels are low in PIH pregnancies [126]. There are clinical exposures during pregnancy because improvement of pulmonary hypertension leads to increased sexual activity and pregnancy. There are only ten reported exposures of pregnant patients to beraprost none with any harm. There is a case report of patients using iloprost in pregnancy [127]. There was no reported harm but this involved only 3 patients. The trouble with this class of drugs is that while they are effective in pulmonary hypertension they are delivered locally through inhalation or intravenously except for iloprost. The oral route seems the cheapest and perhaps the one that would not cause relative diminution in placental bed flow. We need to await the development of drugs that would cause a local increase in prostacyclin production in the placental bed. An additional benefit of iloprost is that it also works through a secondary system PPAR that may reduce vascular smooth muscle hypertrophy. All this class of drugs probably will cause some hypotension. This class of drugs all interfere with platelet aggregation and so bruising or even clinically significant bleeding might occur. The other problem with this class of drugs is that although designed for prostacyclin receptors they also are agonists for all classes of prostaglandin receptor and there is some thromboxane receptor stimulation. So there is limited stimulation of the desired receptors without stimulation of the opposing receptor classes [128].

Leukotriene receptor blockers

There are three drugs in this class. monteleukast, zafirleukast and pranleukast. Monteleukast has been in use for treatment of asthma and recently allergic sinusitis as are the other membranes of this class. Another drug zileuton blocks the production of leukotrienes [129]. These drugs are well tolerated have few side effects and are all pregnancy class B drugs. There are sporadic reports of asthmatic patients taking multiple medications including a leukotriene receptor blocker early in gestation of limb defects. In animal even 110 times the normal human dosage has shown no defects at all during the entire gestation. There is some evidence that preeclampsia increases the concentration of lipooxygens especially 15 HETE on the maternal side [130]. They are also increased in fetal serum from preeclamptic pregnancies [131]. Therefore this class of drugs may reduce fetal placental vasculature resistance.

Thromboxane receptor antagonists

These were first developed in the 1990s to outperform aspirin in platelet aggregation prevention but they were less effective. There are no members of this clinical class in use at present except for terbogrel. This class of drugs is efficacious in PAH [132]. The most likely to be developed is terutroban. It has been used in clinical trials to prevent worsening atherosclerosis. Several others; ifetroban and sulotroban failed to achieve an improvement over other antiplatelet therapies especially when compared to aspirin. If this class is used bleeding precautions used for other blood thinners would have to be followed, so at present this class will not be available to help in PIH.

Thromboxane inhibitors

This is another class of drugs that are early in development because they were first compared to aspirin for thrombosis prevention and were not superior and were much more expensive. Terbogrel which is both a thromboxane production inhibitor and a receptor antagonist has been previously mentioned here for efficacy in treating PAH. This trial was halted after patients had an increase in leg pain compared to the other arm of the trial. The main problem with this class is that blockade of arachidonic acid into the thromboxane synthesis path still allows synthesis of PGs PFs and PHs all of which can interact with their receptor and the thromboxane receptor so this drug class may achieve limited effect.

Rhokinase inhibitors

There is one member of this class, fasudil. This drug has been approved by the FDA for treatment of cerebral vascular spasm and for pulmonary hypertension. It works by inhibiting activated rhokinase which you can see from the ROCK schematic is important in vessel constriction [133,134]. Rhokinase is probably also important in PIH because activated rhokinase downregulates local production of nitric oxide [135]. There is experimental evidence that in a rat model of fetal growth restriction, fasudil returns growth to normal [136]. This drug Is presently unrated but there are no reported harms from patients accidentally exposed to fasudil during pregnancy that are available.

Soluble guanylate cyclase activators

There are two members of this class of drugs available: Cineiquat and riociquat. This class passes downstream of nitric oxide to activate its target. Soluble guanylate cyclase, raising cyclic GMP production intracellularly which is important in vessel relaxation as you can see from the previous schematic. They are both in phase 2 trials for efficacy and toxicity but have so far had low

toxicities and side effects. It will be a while before they are available to use in pregnancy even experimentally but seem to offer theoretical advantages.

Uric acid oxidase inhibitors

Allopurinol is the only member of this class. I mention this class simply because it is being discussed for use in pulmonary hypertension and has a long track record. The question is whether elevated uric acid levels are a marker or are involved in the pathology of PAH [137]. It is a class C drug because long term studies have not been done in humans. There is no reported harm from usage in pregnancy so it is probably safe but I cannot find a logical reason that it should help in PIH but perhaps in the future there will be logical pathophysiologic usage for it. If it proves efficacious in PAH then maybe a trial in PIH should be initiated (Table 1).

New Methods of Monitoring PIH

We need to develop methods that more acutely measure fetal well-being in patients being treated and monitored for PIH and IUGR. The present methods of estimated growth, amniotic fluid volume and Doppler changes in these fetusues do not give us any information except long term and end stage results. Serum markers that are presently known to be associated with PIH and IUGR such as endothelin levels, NO, 15 HETE levels and other markers which we already know are altered and are at least experimentally are used as screening tests for these syndrome need to be followed acutely in patients being monitored for these diseases to see if worsening markers are associated with fetal problems and if improving markers are associated with improving fetal well-being. Urinary metabolites of prostacyclin and nitrous oxide might be used to monitor weekly placental bed health. At present in a population there is a wide range of nitrate metabolites in urine due to a wide range of nitrate intake with food. Adding an arginine supplement should increase the urinary production of nitrates. An individual followed solely by themselves should reduce the effect of diet on this test.

There are also two potential ultrasound markers presently not being used that might give us earlier insight into fetal well-being. The first is the change in diameter of the umbilical cord and the second is umbilical vein flow divided by the estimated fetal weight or estimated fetal abdominal area [138-140]. In this experience the umbilical cord shows a reduction in size prior to reduction in fetal growth rate so it may be a marker for both fetal health and compromise. An umbilical cord which is growing means a fetus that is growing and also the reverse. The measurement of umbilical vein blood flow is easily measured. Measurement of the umbilical artery has failed as a clinically reproducible test. This is probably because it is so pulsatile that measurement of the average velocity is prone to error and also flow along the edge of the vessel is markedly different from the central velocity due to vessel wall interaction. Flow in the umbilical vein is non-pulsatile in the normal physiologic state and the single vessel is large leading to less difference in central and peripheral flow in the vessel. Ideally we would divide the blood flow by the BMI like is done in calculated cardiac output calculated by Fick method but the height is not obtainable in utero because at the present time we are very poor in predicting height and as a consequence even poorer at basically guessing the surface area [141,142]. Calculating the flow by the estimated abdominal area is as close as we can get to this value. This would give a value of centimeters/minute which seems awkward but would give a value of blood flow divided by the most sensitive estimator of fetal size and also the most rapidly changing variable in fetal growth [143].

Summary

There has been a huge increase in our knowledge of the pathophysiology of PIH. It has also been found that early onset growth restriction is related to PIH and probably works in a parallel way. PAH has a similar if not exact same sequence of pathophysiologic beginnings and has many more pharmacologic treatments available some or all of which might be helpful in treating PIH. Early markers for one disease also are markers for the others. Treatments effective as supplements for PIH both in prevention and management should also work for IUGR treatment and prevention. Improvement in maternal health in PIH has not so far led to improvement in neonatal morbidity and mortality. Our immediate goal should be to prolong pregnancies and improve growth in pregnancies complicated by PIH. Even if we were to be able to delay delivery 2 or 3 weeks in these patients it would lead to an immense improvement in neonatal morbidity and mortality.

Learning the actions, dosages, contraindications and best treatment options of a dozen or more new

Table 1: Potential drug classes for therapy in PIH/placental dysfunction.

Drug Class	Potential mechanism	Class members	Pregnancy class
Nitrate donors	NO diffusion	Arginine, nitrates	B
PDE-5 blockers	Increased local NO production	Tadafil, sildenafil, numerous others	B except sildenafil C
Prostacyclin receptor agonists	Reduced vasoconstriction	Iloprost, beraprost	B iloprost beraprost unrated
Endothelin receptor blockers	Reduced vasoconstriction improved endothelial function	Sitaxentan, zilosentan numerous others	unrated

therapeutic classes is not easy but it might lead to unique benefits. Avoiding beta blockers, starting with calcium channels blockers and then adding sympathetic blockade, adding new supplements such as L-arginine and adding drugs from new therapeutic classes in clinical experimental studies and developing more acute methods of determining improving or worsening fetal health will all benefit the babies we care for and might even lead to less maternal morbidity while maintaining maternal mortality improvements developed in the last 30 years.

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Schematic 1: Rhokinase smooth-muscle contraction system.

Calcium ion (Ca^{++}) diffuses in from outside the cell and from the sarcoplasmic reticulum through specific calcium pores that open in response to various, mostly intracellular, signals. The ionized Calcium binds to Calmodulin which changes its confirmation and is able to bind to Myosin light chain kinase, MLCK, activating it, which allows it to phosphorylate Myosin light chain 20 which allows it to activate and bind to actin causing muscle fiber contraction. In the same cell, G proteins, after they interact with their specific ligands, such as endothelin-1, allow the G protein and its associated proteins to take a phosphate group off of guanylyl triphosphate, GTP, forming guanylyl diphosphate, GDP. GDP then binds to Rho A. This in turn allows it to bind to Rho associated C kinase, ROCK. Rock can then add a phosphate to Myosin light chain phosphatase, MLCP, which then becomes inactive, preventing it from deactivating MLC 20 by removing the same phosphate that MLCK added to activate it. In this schematic the striped enzymes are active the unstriped ones inactive.

Schematic 2: Nitric oxide muscle relaxation system.

Nitric oxide is produced in endovascular endothelial cells in response to various stimuli such as shear stress and activating factors. The nitric oxide, NO, which is soluble in both membrane fat and water, diffuses into underlying smooth muscle cells. There it binds to guanyl cyclase, activating it and allowing it to convert, guanyltriphosphate, GTP, into cyclic guanylmonophosphate, c GMP, biphosphate, an inactive wasteproduct. The cyclic GMP, binds to c GMP kinase markedly accelerating its kinase activity. The activated cGMP kinase in turn adds a phosphate group to multiple proteins. This phosphate addition opens some Potassium channels, increases the activity of phospholambin which reduces Calcium release from the sarcoplasmic reticulum, reduces activity of some Calcium channels and reduces the activity of IRAG and phospholipase c B-3, both of which reduce intracellular inositol phosphate 3, IP3. All of these actions lead to a lowered Calcium concentration and an increased Potassium concentration and push the cell towards hyperpolarization. The c GMP is broken down by phosphodiesterase, PDE, of various types in various cells. PDE inhibitors stop this reaction thereby increasing the intracellular concentration of cyclic GMP.