Kofinas Perinatal

Providing Care to the Unborn ®

Alexander D. Kofinas, MD
Director, Kofinas Perinatal
Associate Professor, Clinical Obstetrics and Gynecology
Cornell University, College of Medicine

Deconstructing the value and benefits of "standard of care" concept in obstetrics

Definition

Standard of care refers to treatment modalities of specific diseases that are widely accepted by the majority of physicians, insurance companies and certain health care related organizations. Such standard treatments have evolved over the years as a result of clinical experience, basic science research, clinical research and technical innovation with the goal of leading to uniformly acceptable outcomes. Some of the outcomes are unsatisfactory to many physicians and researchers, but never-the-less these outcomes are accepted because they are the best that can be achieved given available knowledge and expertise. The vast majority of physicians practice in very similar ways on most of the well known and long established conditions and diseases. Of course, this is to be expected, and it is a paradigm that holds true not only for medicine but for all human endeavors where evolution is the key to progress, and where the "minority" is always the catalyst for change.

There are many definitions for the term standard, but the following, I believe, best captures the essence of the word as it stands in medicine: "*A standard is something considered by an authority or by general consent as a basis of comparison; an approved model*." The important point to recognize here is that just because a procedure is standard does not mean that it is "flawless" or that it cannot be improved. Building on this premise, in order to have innovation one must deviate from the norm, and in this case the norm is the "standard of care."

When a physician practices medicine in a manner that deviates from the "standard of care" and his patients' outcomes are inferior to the average doctor's outcomes, then we can safely assume that this physician does not practice according to acceptable standards and that his care is in fact *substandard*. In such cases it is rather easy to identify physicians practicing poor quality of care; but what about when a physician does not deviate from the standard of care, and his or her outcomes are still poor? This, in fact, occurs often since many conditions in medicine have not been well defined in terms of diagnosis, prevention and treatment and there is a lot of room for innovation. Innovation, however, comes not from repeating standard treatments, but by studying standard treatments, identifying where they are inefficient, and in turn finding ways to improve them. A physician that treats his patients with non-standard methods and experiences

consistently superior outcomes to those achieved by the "standard of care" approach should not be censured but embraced. Such advances in medical practice should become the impetus for further research and advancement of our knowledge, not the focal point of bickering and regression. *No one has and no one should be given the authority ever to deny any patient the right to accept new and different treatments when such treatments offer a reasonable chance to improve the patient's condition.* Likewise, no one should have the authority to deny any physician the right to utilize his collective experience, ability to reason, ability to think, and ability to analyze past experiences in order to come up with new ideas and novel treatment approaches. The physician is the lifeblood of medicine. If he is not given the freedom to innovate and jettison ineffective treatment techniques then medical progress will screech to a halt.

Standard of care practices are frequently the result of a collective "herd mentality" and not necessarily based on valuable, verifiable and most importantly, up-to-date scientific evidence. When the majority (physicians, health care organizations, insurances and hospitals) have adopted a particular treatment modality as the treatment of choice ("standard of care") they become very difficult to challenge by any single physician, even if that physician has evidence that contradicts their conclusions, as is the case here. Resistance to change in the medical community is immense and pervasive, as it is throughout human society. As a result of such resistance, a "time honored" but scientifically unproven treatment may, due to pure inertia be employed for many years because it has been accepted by the majority as the "standard of care" despite strong contradictory evidence.

One of the most impressive examples of where employing the "standard of care" can lead to devastatingly worse outcomes than new techniques is in the use of intravenous Magnesium Sulfate for the treatment of premature labor. Magnesium Sulfate treatment has been used for over two decades after it was introduced as a treatment of choice for stopping premature labor without any scientifically valid evidence to support such effect. In fact, magnesium replaced an equally ineffective treatment which was intravenous pure (100%) alcohol. As "funny" as it may sound today, intravenous pure alcohol infusion was the standard of care in the 1970s and early 1980s and it was displaced by Magnesium Sulfate. Over the last decade, several studies have shown that magnesium has absolutely no measurable effect on premature labor inhibition, but does exhibit clear and measurable side effects that can cause and have caused many maternal and fetal/neonatal deaths. At Kofinas Perinatal we have stopped using intravenous Magnesium Sulfate approximately 8 years ago and began treating our patients who suffer from premature labor with safer and more effective oral medications. With such treatments, we have been able to reduce prematurity by more than 50%. In contrast, 99.9% of patients in this country are treated with the standard of care intravenous Magnesium Sulfate and hospitalization. The results of this treatment are dismal and lethal. Prematurity has increased by more than 50% in the last 16 years. We spend twenty-six billion dollars annually for pre-maturity related problems, including prevention, and the obstetrical community can see nothing wrong with that *{The Lancet 2006 Vol 368 July 29, p. 339; Editorial}*.

I have been accused by some insurance plans for not practicing according to standards of care when it comes to prematurity and refuse to pay my weekly or bi-weekly visits, citing them as excessive and unwarranted according to the existing "standards of care". I have however achieved superior results with my treatment modality and at the same time have achieved substantial cost reductions. My vindication has arrived in the form of a recent article by a well respected researcher and high risk specialist in the Journal of Obstetrics and Gynecology, the official journal for the American College of Obstetricians and Gynecologists (ACOG). Dr. Grimes calls the use of Magnesium Sulfate "a North American anomaly" and went on to say "the fact that it remains the most common tocolytic in the US today is unexplained but reflects inadequate progress toward ***rational therapeutics in obstetrics***". Further more, he calls such treatment "***shaky, poor science and worse ethics***." Dr. Grimes attributes such anomalies in part to the unjustifiable, ill-conceived and irrational support for such treatments by authoritative organizations, institutions and poorly critiqued announcements (editorials) in prestigious journals. *{Magnesium Sulfate Tocolysis: time to quit. D. A. Grimes, MD, and K. Nanda, MD, MHS 2006 108;4:986-9}* Such events create an aura of validity that leads to the concept of "standard of care". This "standard of care" then becomes entrenched in the minds of physicians for years to come.

Health care policy today conforms mostly to the utilitarian approach. For the most part this means that we try to achieve the greatest benefit (health, financial etc.) with the least amount of effort and intervention (least cost, complications etc.). This approach requires that we group individual patients into general categories and that we practice based on population statistics. Such an approach has failed because it does not respect the individuality of the patient. It puts life, disease, pain, disability etc. in one basket and attempts to value such qualities collectively without respect for what these qualities mean to each and every one of us. In addition, such an approach ignores completely the fact that the same disease more often than not displays itself in very different ways from patient to patient. Human bodies are chaotic in terms of functionality, and a minor change in one body function might cause immense and completely unpredictable effects on other body functions. Sometimes such influences are beneficial to the individual, but sometimes they are harmful. Beyond our unique biology however, we are individuals with unique characteristics, values, and needs. When we become ill, we expect our doctor to provide us with the highest level of care, the best possible drugs, the best diagnostic technology and the highest level of individual attention. This is what is expected of physicians today and anything less is simply unacceptable. No patient ever will accept to be treated as a unitary member of the "uniform" whole with total disregard for his/her particular characteristics. If Mrs. Doe's fetus dies at 35 weeks, telling her that this happens to 2.2% of all pregnancies after 20 weeks gestation will not comfort her. For Mrs. Doe the chance was 100% and her baby is dead. That is all that matters. In subsequent pregnancies such patients require tremendous emotional and physical support but most of all, they expect the best of care to be provided to their unborn in order to help him/her stay alive and healthy 100% of the time. At Kofinas Perinatal we give such care and support not only to patients that have experienced severe outcomes prior to the current pregnancy but also to those who are at risk for experiencing such outcomes for

the first time. Such high quality of individual care leads to trustful physician-patient relationships, which along with our novel approaches help us prevent most of the poor pregnancy outcomes that would otherwise be achieved by means of "standard of care." With the above in mind, I will try to assess the current "standard of care" employed by obstetricians and high risk experts in the management of pregnancy related complications. I shall analyze each medical condition or pregnancy related complication individually and when indicated in combination with concurrent conditions that may further complicate the pathology involved.

Pregnancy related diseases and complications

Introduction

Before I endeavor to analyze any specific conditions I would like to draw a distinction between pregnant and non-pregnant patients. Non-pregnant patients suffering from any disease can be treated with any approach as far as that particular approach provides more benefit than risk to the patient. Pregnancy is a state where the female patient hosts another human being for nine months. The mother literally and physically surrenders part of her body and a significant part of her functional capacity to the unborn. Without such relationship there would be no reproductive capacity. Pregnancy is a state of "hostile symbiosis". The developing embryo contains paternal genes whose sole purpose is the survival of the embryo in order for these genes to be preserved and pass on to the next generation. These genes attempt and usually succeed to change the functionality of the maternal body in ways not possible otherwise. This process is true across all forms of life and all modalities of reproduction and is known as genomic imprinting. *(David Haig, Genomic Imprinting and Kinship; Rutgers University Press, New Brunswick and London)*.

It has been established for many years now that many if not all of the pregnancy related complications are the result of the constant struggle between the developing embryo and the maternal body functions. Dr. Haig has called such struggle "a silent struggle". This struggle goes on from the earliest stages of pregnancy at the time of conception when the paternal sperm penetrates the maternal oocyte (egg) during the process of fertilization. This struggle remains silent for variable time intervals according to the underlying condition and when it becomes apparent it is too late. The damage has already happened and the outcome varies according to the condition under consideration. The battleground of this struggle is for the most part the developing placenta. The placenta is the single most important organ in human development. The quality of placental development defines the quality of maternal-fetal interaction and subsequently the quality of fetal development.

Pregnancy is a dynamic process that lasts 9 months if all goes well and results in a healthy, well-grown, term neonate. This is the ideal outcome for any pregnant woman. This should be the ideal target outcome for any physician who cares for pregnant women. Unfortunately this is not the case for many women. Of all clinical pregnancies, 25% are

lost prior to 13 weeks and of those that make it past 13 weeks, as many as 30% will be further complicated by some form of maternal or fetal impediment. Further more, 43% of pregnant women experience labor and delivery related morbidity that is unique to pregnancy. *(The Magnitude of Maternal Morbidity During Labor and Delivery, United States, 1993-1997: http://www.cdc.gov/od/oc/media/pressrel/fs030327.htm)*

Pregnancy complications can affect the mother, the unborn, or, as is most often the case, both. The worst outcome possible is maternal and fetal death. Between a normal outcome and the worst possible outcome lay all pregnant women that may experience outcomes with variable degrees of abnormality. This spectrum of outcomes can lead to variable degrees of disease and disability to the mother as well as the unborn. Obstetrics so far has primarily been focused on absolute outcomes. Most of the research in our field has a binary approach to outcomes by utilizing arbitrary cut off points that define normal from abnormal. This may be convenient for statistical purposes but there is nothing further from the truth when it comes to life. Life and for that matter, fetal development is a continuum. It is inappropriate to compartmentalize it in arbitrary and crude ways. Unfortunately this is the result of our inability to clearly distinguish and measure various shades of the abnormal. This has led to a mindset of acceptable mediocrity because it is easier to achieve mediocrity than struggle for perfection when one recognizes that one may never achieve perfection and thus be accountable for the failure. Advances in obstetrics over the past century have helped us achieve significant improvement in outcomes with moderate effort. Maternal mortality remains a global problem yet to be solved since more than 550,000.00 women still die as a result of childbirth annually. *{Department of Reproductive Health and Research*
World Health Organization, Geneva 2004; WHO_UNICEF_UNFPA maternal mortality in 2000.pdf}. The biggest killers of mothers and babies in the past were the following conditions:

1. Maternal hemorrhage
2. Maternal puerperal infection
3. Dystocia due to fetal malposition and size.
4. Prematurity
5. Pre-eclampsia

Advances in blood banking methodology have saved countless maternal lives. Antibiotics contributed significantly to almost elimination of maternal puerperal infection related deaths. Improved surgical techniques have made it possible to employ cesarean section as a maternal life saving birth modality and decreased maternal mortality further more. Prematurity was and remains one of the most common reasons for neonatal death despite significant reductions in neonatal deaths with the introduction of Neonatal Intensive Care Units (NICU) in the mid 1960s. Pre-eclampsia is now one of the most common reasons for maternal death despite significant improvements in the management of such patients. Since 1982, maternal mortality has not declined; in contrast, there is a slight increase in maternal deaths in the recent 5 years. More than half of maternal deaths can be prevented with existing interventions. In 1997, 327 maternal deaths were reported based on information on death certificates; however, death certificate data underestimate these

deaths, and the actual numbers are two to three times greater. The leading causes of maternal death are hemorrhage, including hemorrhage associated with ectopic pregnancy, pregnancy-induced hypertension (toxemia), and thromboembolism. Based on the most resent statistics compiled by the World Health Organization the maternal mortality in the developed countries, including the United States, is 20 deaths per 100,000 live births. This is a very high number and the saddest part is that over the last several years it has increased. However, the increase is most likely due to better reporting and data collection quality. In the past, only one third of the maternal deaths were reported as such. The least one can say, is that we have made no progress in saving maternal lives in the last 10-15 years. *{CDC_Natality stats_2002.pdf, and WHO_UNICEF_UNFPA maternal_mortality_in_2000.pdf}*
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4838a2.htm
http://www.unicef.org/pon96/leag1wom.htm
http://www.childinfo.org/areas/maternalmortality/maternal_mortality_in_2000.pdf

This figure is substantially higher in less developed countries. Accurate morbidity figures however are not available due to logistic difficulties in recording and evaluating the financial and health impact of maternal and fetal morbidity. One thing that is clear so far in our specialty is the fact that we have not found a way yet to prevent or diagnose the above conditions early and thus achieve complete cure and so avoid the related complications that still devastate a lot of patients and their babies. We have so far only been able to develop approaches to treat the conditions after they develop and thus we are by definition forced to accept partial and inferior treatments that lead to inferior outcomes.
Because of significant gains in outcomes over the past century with relatively small efforts as noted above, we are at a stage where very little and some times not measurable improvement in outcomes takes disproportionately more effort on the part of the obstetrician (Pareto's Law). This is a heavy burden for all of us who daily struggle to add our small building block on the "monument" of improved maternal and fetal health. What makes pregnancy all that important for mankind is clear evidence from recent research that the quality of fetal development during the nine months of pregnancy defines the total health and quality of life for the duration of the neonate's life expectancy in adulthood. *(Early Human Development: Volume 81; 2005, New England Journal of Medicine, 353; 17:2005, New England Journal of Medicine 351;21: 2004).*
Adulthood diseases such as obesity, hypertension, diabetes, heart disease, stroke, premature organ failure etc. have their origins in fetal life. Poor fetal development during the nine months of pregnancy leads with increasing frequency to the above mentioned conditions that plague our modern societies. It is inconceivable how can anyone ignore the above facts or simply be indifferent regardless of reasons. As a society we have come a long way and we are at the inflection point were longevity is linked to disease and suffering. The financial and emotional burden to our society is increasing exponentially and the medical community seems to be paralyzed. From my point of view as an obstetrician I fight my own war against these pregnancy associated maladies and with hard work, research and new and innovative approaches to old problems I have managed to reduce measurably and significantly the complications that can cause the above long

term conditions by being able to prevent such conditions to begin with, instead of the old "standard of care" approach of treating them after they manifest in full force.

My practice is heavily focused on few specific high-risk conditions. These are the following:

1. **Pregnancies conceived by means of Artificial Reproductive Technologies such as in-vitro fertilization and ovulation induction.** Such pregnancies are complicated by poor fetal growth (intrauterine growth retardation) and prematurity at a rate 3 times the average or more. For singletons (pregnancies with one fetus only), studies with matched controls indicated a relative risk of 3.27 (95% confidence interval 2.03 to 5.28) for very preterm (< 32 weeks) and 2.04 (1.80 to 2.32) for preterm (< 37 weeks) birth in pregnancies after assisted conception. Relative risks were 3.00 (2.07 to 4.36) for very low birth weight (< 1500 g), 1.70 (1.50 to 1.92) for low birth weight (< 2500 g), 1.40 (1.15 to 1.71) for small for gestational age, 1.54 (1.44 to 1.66) for caesarean section, 1.27 (1.16 to 1.40) for admission to a neonatal intensive care unit, and 1.68 (1.11 to 2.55) for perinatal mortality. Additional and similarly controlled studies presented similar or worse outcomes for such pregnancies. Considering the devastating complications and death caused by growth failure and prematurity is enough to concentrate all our efforts in such patients. More so, considering the long term effects on adult health of those neonates that survive it is a lot more important to use unlimited resources in preventing such complications. *{BJM 2004 Jan 31;328(7434):261. Epub 2004 Jan 23rd., N Engl J Med, 2002 Mar 7;346(10):731-7, Obstet Gynecol, 2004 Mar; 103 (3):551-63, ART outcomes References.pdf}*. In addition, the average age of pregnant women who conceive with assisted reproductive technologies is above 35 years and this contributes further to the risks for poor perinatal outcomes.*{Am J Obstet Gynecol 2006; 194:840-5 (Fetal Loss\Stillbirth Rates in Older women.pdf}*
2. **Patients with known thrombophilic disorders with or without history of pregnancy loss.** Such pregnancies are at risk for various pregnancy complications including fetal loss. In fact, in a prospective study on thrombophilia outcomes across several European countries (multicenter study) it was found that as many as 46.7% of women with thrombophilia experienced fetal loss in comparison to 23% in the control group. The rate of stillbirth in patients with thrombophilia was reported to be from 3.6 to14.3 times higher than the controls. Patients with multiple thrombophilic factors presented with the higher rates of fetal loss and stillbirths. *{European Prospective Cohort on Thrombophilia and in a control group. Lancet 1996;348:913-16, N Engl J Med 2000;343:1015-18, Lancet 2003; 361:901-908}*
3. **Patients with previous fetal loss for a variety of reasons.** Of all clinically recognized pregnancies, more than 25% are lost in the first 12 weeks of pregnancy. Patients who experience fetal death after 10 weeks in a previous pregnancy have only a 25% chance to take a live born home in their next pregnancy. This means that 75% of subsequent pregnancies end up with a poor outcome of either embryonic death, fetal death or neonatal death. Controlled

studies have shown that in patients with thrombophilia 4.4 % of fetuses that are alive at 24 weeks gestation die between 24 and 42 weeks. This is 2X the rate of the control population. Together that means that even the so called normal pregnancies have a fetal demise rate of 2.2% after 24 weeks. This happens when patients are treated under the acceptable "standard of care". Considering that there are 4.5 million births in the United States alone, this translates to 90,000 losses of viable fetuses annually. This is a dismal record and according to our experience uncalled for since the vast majority of such losses are preventable with our novel approaches. Fetal loss after 24 weeks at Kofinas Perinatal is almost zero percent. In more than 4000 high-risk pregnancies over the last 7 years, our expected fetal death rate according to the "standard of care" approach would be approximately 200. In contrast, we have only lost two babies from well documented umbilical cord accidents that could not have been prevented unless we were present at the time of the event. *{Obstet Gynecol 2004; 104: 521-6, (1 Poor OB outcomes w Prior fetal loss after 10wks.pdf) Gynecol Obstet Invest 2006;61:167-170, (Early Pregnancy \Previous1st trim loss Poor outcomes.pdf)}.*

4. **Patients with history of incompetent cervix and pregnancy loss.** Such patients suffer usually from a combination of preterm labor and cervical insufficiency. Such patients have usually lost babies previously under expert high risk specialists and we help them take a healthy baby home. The reason here is the fact that we consider cervical insufficiency (incompetence) as part of the whole that defines the risks for preterm birth. This includes variable degrees of cervical insufficiency mixed at various proportions with preterm labor. Standard of care practice brakes down this condition into two separate and distinct conditions that are treated completely differently. In fact the two treatments are mutually exclusive. If the diagnosis is cervical insufficiency, the standard of care is to not use labor stopping medications and if the diagnosis is preterm labor, the use of cervical cerclage (surgical closure of the failing cervix) is contraindicated. The result is that only a tiny fraction of the patients that deliver prematurely have been treated appropriately. The vast majority of such patients are treated only in part (either for incompetence or only for preterm labor) and for this reason they fail to achieve a normal outcome as defined by a healthy newborn, which is born at term (after 37 weeks of gestation) and is well developed. We have realized in the early 1990's that cervical shortening documented with transvaginal ultrasound leads to preterm delivery; the shortest the cervical length the earlier the gestational age at delivery. Soon after, a large number of investigations confirmed our findings. In a recent study, Fox et al demonstrated that when the cervix is short on transvaginal ultrasound and gets shorter in a follow up ultrasound one week later, 60% of the patients are delivered prior to 37 weeks and an astounding 28% are delivered before 34 weeks. We have known this as early as 1994 and in response we developed a protocol that in such patients, it reduces the prematurity to less than 6%. This is even more valuable considering that our patients are patients with additional prematurity risk factors unlike the ones reported by Fox et al who were low risk patients seen for routine ultrasound. *(Fox et al. Short cervix: significance of follow-up measurement. Ultrasound Obstet Gynecol 2007;29:44-46).* We have

been able to achieve such improvements in outcomes because we look at the pregnancy as a whole with complete understanding of the uteroplacental condition which can only be assessed with Doppler ultrasound. Placental health is important for healthy pregnancy and unless we assure a healthy placental development, we will fail to improve the outcomes. Fragmentation of pregnancy into smaller segments of interest is harmful and delays the progression or our understanding and treatment of pregnancy complications. For the same reason, any particular index of blood flow measurement in the placenta and the fetus has failed to achieve success in preventing adverse outcomes that one can achieve by focusing on the fetal-placental and maternal unit as a whole. This is exactly the reason why we have improved the outcomes of our high risk patient to such a great extend. In addition, the assessment of fetal heart function by means of fetal cardiac Doppler (color and pulsed wave) allows us to utilize powerful medications to stop labor without having to admit the patient to the hospital. With our protocol on preterm labor and short cervix we have been able to reduce premature deliveries from spontaneous preterm labor to less than 6% and to extend the pregnancy an average of 17 weeks from the moment of the diagnosis. Most protocols of "standard of care" practices may prolong the pregnancy by a few hours to a few days just enough time to administer steroids to the fetus for enhanced lung maturity. *{Lancet 2004; 363: 1849-53, Am J Obstet Gynecol 2000;183:830-5,Curr Onin Obstet Gynecol 2005;17:574-78, Am J Obstet Gynecol 2006;194:1-9, Cervix\Cerclage reappraisal Controversy.pdf, cerclage_randomized.pdf, cerclage_randomized 2.pdf, Cerclage when to do it Althusius.pdf, Romero on cervical incompetence.pdf}*

5. **Patients with placental thrombosis (intrauterine blood clots).** Numerous studies have shown that such patients were found to have poor outcomes including early pregnancy loss, fetal loss in the second and third trimesters, intrauterine growth failure with all its consequences, preeclampsia, preterm premature rupture of the membranes (pPROM), preterm delivery and abruption. Such outcomes we found are preventable if patients with uterine bleeding and placental clotting are treated with anti-thrombotic medications as soon as the diagnosis is confirmed. The poor outcomes reported in the literature happen because the 'standard of care" in patients with vaginal bleeding and placental clotting during the first trimester dictates that we do nothing because such findings are c/w threatened abortion. The standard management of threatened abortion is to do nothing and weight for nature to take its course. If the pregnancy fails it is considered an act of God. If pregnancy continues, then the probability of adverse outcome is significantly higher. There is no work up recommendation and there is no standard treatment for such patients. At Kofinas Perinatal we differ. We find the cause of such maladies and treat them accordingly and as long as the baby is normal without genetic defects, the pregnancy is almost certain to be a successful and healthy one. *{Obstet Gynecol 2005;105:339-44, Obstet Gynecol 2003;102:94-100, Am J Obstet Gynecol 1998;178:336-40}* In the past it was only after fetal death that we discovered that the placenta of the dead baby was damaged by thrombosis (blood clots). When the size of the clot exceeded 3 cm in

size it was associated with poor perinatal outcomes. *{Naeye, R.L., Placental infarction leading to fetal or neonatal death. A prospective study. Obstet Gynecol, 1977. 50(5): p. 583-8.}* Recent advances in ultrasound and Doppler technologies allow us to identify such placental thrombotic lesions early in pregnancy and thus intervene for the benefit of the fetus. *{ Am J Obstet Gynecol 1998;178:336-40, Obstet Gynecol 2005;105:339-44, Fertility Sterility 2003;79 (1):100-106, Am J Obstet Gynecol 2004;190:745-50, Seminars in Thrombosis and Hemostasis 2001; 27 (2):107-113Early Pregnancy\1 IVS Flow Normal & Abnormal Janeaux.pdf, Placenta\1 Subhorionic clots 1st thrim Poor outcomes 2.pdf, 1 -SecTrim bleeding Poor outcomes Placenta .pdf, 1 Threatened ab 1st trim poor outcome FASTER STUDY .pdf, 1 IVS coagulation leads to IUGR.pdf}*

6. **Patients with history of preterm birth.** The risk for recurrence is 30-60%. This group includes also the patients that are newly diagnosed with preterm labor. The standard of care has yet to make any progress in preventing prematurity in such patients. It is very well known and established that premature neonates are almost always growth deficient due to placental insufficiency. This brings us back to the fact that most of the pregnancy related complications are associated in one or another way to the placenta. In addition, the cervix has to fail one way or another before a patient goes into premature labor and premature delivery. At Kofinas Perinatal we have achieved to prevent such deliveries with tremendous benefits to the babies, mother and significant cost reductions, both short and long term. We were able to achieve such improvements in outcomes only by looking at the pregnancy as a whole, fetus, placenta and mother. Scheduled cervical assessments, fetal placental and maternal uteroplacental Doppler help us detect placental problems early and thus correct them. This provides a healthy intrauterine environment that contributes to the reduction of most pregnancy related complications including preterm birth. Patients who go into labor despite our efforts, are treated according to our outpatient treatment protocol with Indomethacin / Procardia combinations and we manage to get them to term. We are able to employ such cost effective outpatient treatments due to our expertise and Doppler technology that helps us monitor the fetal cardiovascular side effects of these powerful but potentially harmful medications. *{N Engl J Med 2003;348:2379-85, Preterm Labor\17-a-hydroxyprog-PTL Meis.pdf}*
7. **Patients with history of preeclampsia (high blood pressure during the pregnancy) and poor pregnancy outcome.** Such patients have a 30% to 54% risk to develop preeclampsia in subsequent pregnancies. Preeclampsia remains one of the most common causes of maternal and fetal death, and is preventable in most of the patients at risk with anticoagulation therapies. The recurrence of preeclampsia is the result of underlying chronic vascular problems that manifest themselves as poor placental vasculature. Regardless of the etiology, the fetal and maternal complications are the direct result of poor placental vascular development and dysfunction. Only Doppler Ultrasound can detect such problems. We are able to do so and took the problem one step further; we have reduced pre-eclampsia to a minimum by helping to promote healthy placental development. Others have also shown that preeclampsia can be prevented with

anti-thrombotic treatment like the one we use with our patients. Our goal was not to prevent pre-eclampsia but to secure healthy fetal development. The rest of the benefits were icing on the cake. *{Hypertension 2005;45:86-91, Gynecol Obstet Invest 2002;53(1):22-7, Preeclampsia\ 1 Lovenox prevents PE.pdf}*

8. **Patients with previous pregnancy complicated by fetal growth retardation.** The recurrence risk for such patients is almost 100% because the underlying reason is maternal chronic pathology that affects the placenta. Such pathology is almost always linked to vascular endothelial disease and vascular thrombosis. This in turn affects the quality of the maternal and fetal placental circulation by its propensity to form excessive clotting and vessel occlusion. The increased tendency to clot may be the result of pregnancy alone but most of the time it is the result of preexisting hemostatic abnormalities that are exaggerated by the pregnancy effect upon the hemostatic system. This is the staple of placental insufficiency that finally leads to most of the pregnancy related fetal and maternal complications as has been explained in the previous sections of this document. *{Paediat Perinat Epidemiol 1997 Jan;11 Suppl 1:119-29}*
9. **Threatened abortion: a risk factor for poor perinatal outcomes.** Weis J et al, reported on the increased incidence of adverse perinatal outcomes in patients with threatened abortion. (American Journal of Obstetrics and Gynecology (2004) 190, 745-50) This is a population based study which showed clearly that patients with threatened miscarriages have significant and substantially increased risk to experience poor perinatal outcomes as defined by fetal loss, intrauterine growth failure with all its consequences, preeclampsia, preterm premature rupture of the membranes (pPROM), preterm delivery and abruption. The relative risk for such complications is as much as 4 (four fold increase in the risk). For example, an 8% risk for premature rupture of the membranes becomes 32%. Considering that pPROM is responsible for 30% of all premature neonates and that 80% of all neonatal morbidity and mortality is caused by prematurity, the devastation caused by this risk is immense. Similar findings were presented by E. Johns and Eric Jaunniaux (Obstet Gynecol 2006;107:845–50). The solution for this problem is elusive to mostly everyone. At Kofinas Perinatal with our management protocols have reduced the risk of PROM to less than 1%. With close follow up and careful evaluation of the placenta with high resolution ultrasound, power color Doppler and pulsed-wave Doppler we are able to identify the problems and their etiologies early in pregnancy and at a time that with appropriate treatment we can turn a failing pregnancy into a healthy and successful term pregnancy with a well developed neonate. Our total pregnancy loss after we see the patient at 5 weeks gestation is only 4%. This compares very favorably with the reported in the literature that ranges from 25-35%. About 15-20% of these losses happen in the first trimester and the rest of them in the second and third trimesters. What makes our results profoundly better is the fact that 80% of the few pregnancies that we loose are the result of genetic chromosomal anomalies that are not compatible with life. In other words, we loose an extremely small number of pregnancies that may be preventable.

More than 80% of my practice is focused on the above conditions which are of the highest risk for adverse perinatal outcome.

The rest of the patients fall into a wide variety of high risk condition such as prenatal testing for genetic disorders, diabetes, chronic hypertension, oligohydramnios, fetal anomalies, bleeding etc..

Below are some examples of the difference in management of certain high-risk conditions according to our approach in comparison to the "standard of care" approach employed by the vast majority of specialists in America.

Preterm labor management:

The management of preterm labor consists primarily of an effort to inhibit preterm labor after it has started. Preterm labor is defined as progressive cervical shortening and / or dilatation in the presence of uterine contractions prior to 37 completed weeks of gestation. If there is progressive shortening of the cervix in the absence of contractions the condition is characterized as cervical incompetence (insufficiency). When preterm labor is diagnosed the patient is admitted to the hospital in the intensive care unit of the obstetrical ward and treated with intravenous magnesium sulfate ($MgSO_4$). This is a medication that is expected to stop the patient's contractions. Well conducted studies have demonstrated that magnesium is good for stopping labor for up to 24 hours but not longer. In such patients by delaying delivery by 24 hours we can inject to the mother steroids in order to help the baby's lungs and improve neonatal outcomes. This is the positive of what magnesium has to offer. However, this is a dangerous medication as the risks outlined below indicate. The harm caused by this medication far exceeds the benefits offered by its use.

1. Magnesium has been shown to delay delivery for 24 but has never been shown to prevent prematurity which is the desirable and valuable outcome. Magnesium is a lethal medication if the therapeutic levels are exceeded. Overdose causes paralysis of the respiratory muscles and death by suffocation. To avoid such events, the medication is administered by infusion pump. Infusion pumps are electronic devices that remain unattended for several hours at a time and if they malfunction, can cause maternal death. Human error may also cause improper function of the pump that can lead to maternal overdose. In addition, premature neonates born with magnesium in their blood are up to 3 times more likely to die than similar age premature neonates that have not been exposed to magnesium. As many as 5,000.00 premature neonates die annually because of inappropriate magnesium usage. This is a crime against humanity committed in the name of "standard of care". *{Magnesium Sulfate Tocolysis: time to quit. D. A. Grimes, MD, and K. Nanda, MD, MHS 2006 108;4:986-9}*
2. The cost of administering magnesium is in the range of $2000-$4000 per day, since such management is considered an obstetrical intensive care management.
3. If the labor stops and the treatment is considered successful, the patient is discharged home for complete bed rest. There are two usual and customary ways to treat such patients at home.

a. Home uterine monitoring alone at a daily cost of $800-$1,200.
b. Home uterine monitoring with Terbutaline pump at a cost of about $300 per day in addition to the above daily cost as noted in (a).
c. Daily home uterine activity monitoring generates a lot of false alarms due to the presence of innocent contractions that cannot be distinguished from the preterm labor contractions. This causes an enormous number of emergency visits to the obstetrical emergency unit with enormous obvious and hidden costs. The worst part of such monitoring however is the fact that patients and physicians alike grow tired quickly from the many false alarms and eventually stop responding to such alarms. When labor is finally real, the patient fails to respond and the outcome is another preterm neonate. The fact that despite extensive use of such monitoring prematurity is still climbing is revealing of its negative practical value.

With the standard of care management outlined above one would expect to have substantial improvement in outcomes given that all obstetricians agree that this is the best way to care for this pregnancy complication. Below I will present all the evidence that the above treatment scheme has failed us miserably and we still continue to value it as the gold standard.

Preterm birth rate for all pregnancies in the US in 1990 was 8% *(CDC natality statistics*). At that time, the CDC and NIH along with the Human Health Services department issued an initiative to combat prematurity and reduce it by the year 2000 to 5%. This is part of the healthy people 2000 initiative designed by the CDC and HHS. *{U.S. Department of Health and Human Services Public Health Service Centers for Disease Control and Prevention, [CDC_HHS Healthy People 2000 initiative.pdf]}*. This initiative has failed completely and instead of reducing prematurity to the above noted desirable level, it increased it to 12.5% in 2004 and the predictions for 2006 exceed 13%. *{Pediatrics 2006;117;168-183}*.

At Kofinas Perinatal we treat patients a lot differently. In 1998 we realized that magnesium sulfate does not stop labor and does not prevent prematurity. In addition, we became aware of studies indicating that magnesium sulfate increases neonatal mortality. This certainly convinced us to reject the “standard of care” treatment and look for alternative treatment modalities that will be not only more efficient but also safer. At the time, there was good scientific evidence that Indomethacin, an anti-inflammatory medication is a powerful tocolytic and safe if used according to strict guidelines. Indomethacin was found to prolong pregnancy and reduce the number of premature births unlike magnesium sulfate. In addition, Nifedipine (a smooth muscle relaxant) was found also to be safe and efficacious in stopping premature labor. Based on the existing scientific evidence, our advanced technological infrastructure, our clinical expertise and our previous research on the matter, we devised the Kofinas Perinatal protocol for the management of preterm labor and prematurity prevention. This protocol was modified over the years according to emerging knowledge in order to fine-tune it; the result was a substantial reduction in prematurity with excellent outcomes and non-existent maternal and fetal complications. Patient education is pivotal in the management of preterm labor and prematurity prevention. We achieve such education with written material produced

by Kofinas Perinatal and continuous education during each and every visit. The patient becomes an active component of the treatment protocol and the caring physician is available to the patients 24/7 with immediate responses to all patients' calls. **{King, J.F., et al., *Calcium channel blockers for inhibiting preterm labor (Review).* Cochrane Database of Systematic Reviews, 2003. Art. No.:CD002255(1): p. 1-50, Crowther, C.A., J.E. Hiller, and L.W. Doyle, *Magnesium sulphate for preventing preterm birth in threatened preterm labour (Review).* Chochrane Database of Systematic Reviews, 2002. Art. No.: CD001060(4): p. 1-106, Vermillion, S.T. and C.N. Landen, *Prostaglandin Inhibitors as Tocolytic Agents.* Seninars in Perinatology, 2001. 25(4): p. 256-262 Respondek, M., S.R. Weil, and J.C. Huhta, *Fetal Echocardiography during indomethacin treatment.* Ultrasound Obstet. Gynecol., 1995(5): p. 86-89, Magnesium Sulfate used for indications other than pre-eclampsia is associated with excess total perinatal and pediatric mortality. As a result it is estimated that as many as 4800 infant deaths are attributable to the use of magnesium *Obstet Gynecol 1998;92:308-11}***

Management of patients conceived by means or ART

Such patients have been traditionally treated as normal low risk patients unless they suffered from preexisting conditions such as chronic hypertension, diabetes etc. in which case attention is paid to manage such complications. As a result such pregnancies continue to be complicated by some of the most damaging fetal conditions such as preterm birth, growth failure and neurological damage. It was not until recently that other researchers started viewing ART pregnancies as high-risk pregnancies. A plethora of studies have shown that such pregnancies are at increased risk for fetal loss (only 40% - 60% of ART pregnancies with documented fetal viability at 7 weeks gestation deliver a live-born and even less take a live baby home), a 2-3 fold for SGA and IUGR pregnancies and a similar increase in prematurity. What makes it worse than what it appears to be is that these outcomes happen to singleton gestations. Multiple ART gestations are as much as 10 times more likely to have the above-mentioned adverse outcomes. Singleton pregnancies conceived with assisted reproductive technologies (ART) are at increased risk (25-40%) for prematurity, Very low birth weight, perinatal mortality, growth restriction, pregnancy induced hypertension and placenta previa; these risks are on average 2-4 times the average national risk for such complications) ***{J Obstet Gynaecol Can 2005 May;27(5):449-59},{BMJ 2004 Jan 31;328(7434):261},{Obstet Gynecol 2004 Mar; 103(3):551-63},{Obstet Gynecol 1995 Aug;86(2):188-92} {Fertility and Sterility 2006; 86(5):1356-64},{Twin Res. 2000 Mar;3(1):2-6.}*** It has started to become obvious to most at this point that the poor outcomes with ART patients are due to the associated underlying pathologies that lead to the infertility to begin with and not the ART procedures. Such pathologies are almost exclusively related to various coagulation system imbalances, which cause either complete implantation failure/infertility or partial failure with variable degrees of subsequent placental insufficiency that leads to the above mentioned pregnancy complications. In our experience, 98% of infertility patients have one or more coagulation imbalances and 99% or our patients with previous pregnancy

loss regardless of trimester have usually multiple coagulation imbalances. These findings of ours have been confirmed by others who found that up to 94% of patients suffering from recurrent pregnancy loss and infertility test positive for hemostatic abnormalities (genetic and auto-immune). ***{Hematology/Oncology Clinics of North America 2000;October: 1117-31}*** Such patients when treated with anti-thrombotic treatment (Aspirin and / or LMWH) do extremely well. In our experience the total pregnancy loss of such patients from 5 weeks gestation prior to any evidence of viability is only 4%. Of importance is the fact that 80% of these losses are documented lethal chromosomal abnormalities. This means that the loss of potentially normal pregnancies is such patients is only 1% or less. Other researchers have reported similar outcomes. ***{Hematology/Oncology Clinics of North America 2000;October: 1117-31}*** We achieve such success only because we treat all such patients according to our thrombosis management protocol. In brief, we see these patient every two weeks and we assess the placental development with high resolution ultrasound, power color Doppler and pulsed wave Doppler of fetal and maternal placental vessels. The overall progression of placental development is monitored and manipulated towards achieving the best placenta quality possible. (Such a placenta is a placental without or with minimal thrombotic lesions, intact intervillous space flow, minimal or none fetal thrombotic vasculopathy and normal uteroplacental arterial compliance with as low resistance as possible). Because placental pathology (like any other human pathology) is a continuum and not a dichotomous state, there is a spectrum of various degrees of placental thrombotic pathology that lead to adverse outcomes ranging from infertility to 1st trimester embryonic loss, 2nd trimester fetal loss, fetal growth failure, preterm birth, late fetal loss and neonatal death. Like-wise, all surviving neonates that experienced any of the above complications suffer from life-long physical and mental developmental delays. ***{Blood 2003;101:4850-52},{Blood. 2002;99:2606-08}, {Am J Obstet Gynecol 2001; 185:1059-63}, {Obstet Gynecol 2005;105:339-44}, .{Prenatal Diagnosis 2001;21:658-61},. {Seminars in Thrombosis and Hemostasis 2001 Vol:27(2):101-110},{Placenta 1995; 16:165-170},{Seminars in Thrombosis and Hemostasis 2003; 29(2): 213-16}{Seminars in Thrombosis and Hemostasis 2001; 27(2): 107-113}, {N Engl J Med 2002; 347(1):58-59}, {Seminars in Thrombosis and Hemostasis 2003; 29(2): 175-183}***

Management of patients with non-genetic recurrent pregnancy loss in the first trimester

Such patients are very much like the ART patients. They for the most part are a different expression of the same underlying coagulation problem that affects placental development. Almost 100% of such patients have multifactorial hemostatic imbalances. Such imbalances are more likely to cause variable degrees of placental thrombosis with all its consequences. In such patients the standard of care attitude is expressed by the following common obstetrical statement "…it was meant to be. Do not worry. It will all be fine next time." We have seen patients who experienced as many as 12 such losses and were never given a scientific explanation. With proper diagnosis, established plan of treatment and monitoring such patients have successful healthy pregnancies 98% of the time if they conceive a chromosomally normal fetus. Our treatment plan requires

planning of the pregnancy, ovulation confirmation, and evaluation of endometrial receptivity and initiation of anti-thrombotic treatment as soon as ovulation is confirmed. In the course of the pregnancy, many of these pregnancies evolve normally with normal uteroplacental and fetal-placental circulations. However, as many as 40% of such patients demonstrate poor placental vascular compliance despite the treatment. Such lack of proper response is identified at its earliest stages and dealt with by treatment modifications. The effects of such treatment modifications are monitored according to our thrombosis management protocol with high resolution ultrasound of the placenta, power Doppler of placental intervillous space and pulsed wave Doppler of fetal and maternal placental vessels. Such monitoring defines the bioavailability of LMWH in each particular patient since we have long ago noticed that patients with similar and appropriate LMWH levels (anti-Xa activity in patient's plasma) experienced significantly different responses in prevention of placental thrombosis. As mentioned elsewhere in this document we evaluate every pregnancy loss that happens under our management. Our total pregnancy loss after a documented pregnancy at five weeks with a gestational sac but not evidence of viability yet is only 4%. Of such losses, 80% are documented chromosomally abnormal with aneuploidies incompatible with life.

Management of patients with 2nd trimester loss (fetal demise of unknown etiology), fetal loss from pPROM, fetal loss with "incompetent cervix with cerclage failure", fetal loss after multiple episodes of 1st and 2nd trimester bleeding that was not investigated properly, late fetal loss with placental findings, history or IUGR with or without history of preterm birth in previous pregnancy is mostly similar to the management of the above conditions with minor variations.