Kofinas Perinatal

Providing Care to the Unborn ®

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Protocol for the management of pregnancies conceived by ART

Introduction:

Infertility affects 10% of couples. Although there are many causes for infertility, the vast majority relate to maternal problems regarding ovulation and implantation. Almost 50% of infertile couples do not suffer from infertility but inability to have a successful implantation (after normal conception, the embryo fails to implant due to maternal problems). These problems are either vascular in nature and relate to the quality of the endometrial vasculature or the result of immune system problems. The most common condition that affects the quality of placental vasculature formation is thrombophilia. Thrombophilia is both genetic and autoimmune in origin. Approximately 94% of patients with very recurrent pregnancy loss and infertility suffer from one or both types of thrombophilia and with proper treatment achieve successful pregnancies. ***{Hematology/Oncology Clinics of North America 2000;October: 1117-31}*** However, infertility and recurrent pregnancy loss is only one of the clinical manifestations of such patients. Even after successful early pregnancy, patients who suffer from thrombophilia and conceived with ART are subject to serious pregnancy complications because of deficient placental formation. These complications are a continuum of the infertility/ recurrent early pregnancy loss syndrome and they are manifest in the form of second trimester fetal demise, third trimester fetal demise, fetal growth failure (IUGR), preterm labor, and preterm delivery from either preterm labor or incompetent cervix. The common denominator of the above complications is a poor placental formation due to disturbed coagulation mechanism (excessive clotting and/or hypofibrinolysis). Such disturbances interfere with the process of trophoblastic conversion of the uterine endometrial spiral arterioles. Poor trophoblastic conversion leads to a deficient placenta formation which in turn causes the above complications as well as many of the hypertensive disorders of pregnancy (PIH and HELLP syndrome). At Kofinas Perinatal, we have been treating such

pregnancies since 1994 when our intramural research revealed increased incidence of adverse outcomes in such patients along with increased incidence of placental thrombosis. Most recently several studies from American and European institutions have confirmed our findings and demonstrated the increased risk for adverse perinatal outcomes in such patients. ***{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}, {Twin Res. 2000 Mar;3(1):2-6.}*** At Kofinas Perinatal, we were able to reduce the prematurity of such patients from as high as 30% to less than 5% by implementing the following protocol.

Management of ART pregnancies

All patients with ART pregnancies are seen for the first visit at 5-6 weeks for careful assessment of the early placental development and to R/O chorionic tissue degeneration/subchorionic clot formation. Next visit is in 7-12 days depending on the presence or absence of fetal heartbeat. Since most of these patients are already treated for thrombophilia, assessment of appropriate anti-Xa activity is documented. If levels are not therapeutic or if the placenta does not respond, the dosage and/or the frequency of treatment is increased. Starting dosage is 40 mg SC qd and it may be increased to as much as 60 mg BID if indicated. Any treatment adjustments are correlated with maternal anti-Xa levels as well as placental quality. Deteriorating placental pathology in the presence of acceptable anti-Xa levels indicates reduced Lovenox **bioavailability** and the dosage is adjusted upwards until the placental condition is improved.

Subsequent visits are every two weeks. Wider intervals between follow up visits may be associated with extensive and irreparable placental damage.

The visits involve the following:

1. Assessment of major fetal and maternal placental vessels with color and PW Doppler. (Uterine arteries, subplacental spiral arterioles and umbilical arteries).
2. Assessment of fetal chorionic villi and the intervillous space with high resolution high magnifying power grey scale imaging combined with high definition power color angio. (This imaging identifies evidence of fetal chorionic damage at the earliest possible stage and when it is still treatable). In addition, this methodology is useful in the determination of fetal thrombotic vasculopathy (FTV) and intervillous

space (IVS) thrombosis which may lead to placental thrombosis and fetal compromise. ***{Seminars in Thrombosis and Hemostasis 2003; 29(2): 175-183}, {N Engl J Med 2002; 347(1):58-59}, {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}***

3. Fetal anatomical and growth assessment.
    a. Decline in fetal growth rate is treated with upward adjustment of the antithrombotic treatment as indicated even if the anti-Xa activity level is in the normal range. Fetal growth deceleration (declining trend in two consecutive visits two weeks apart) in the absence of gross thrombosis is suggestive of poor IVS circulation and usually responds well to increased amounts of Lovenox.
4. Assessment of maternal uteroplacental arterial compliance with progressing gestational age. Doppler of the uteroplacental circulation is instrumental in defining the state of compliance of the uteroplacental vessels. ***{Seminars in Thrombosis and Hemostasis 2003; 29(2): 213-16}***
5. Cervical assessment for evidence of shortening, inclusion cysts that may compromise cervical integrity, and for funneling until 24 weeks and after that only if the patient reports preterm labor symptoms or signs. Cervical length is inversely proportional to the risk for prematurity. ***{N Engl J Med 1996;334:567-72}, {Am J Obstet Gynecol 1995;172:1097-106}, Am J Obstet Gynecol 1993;188:586-96***
6. Assessment of lower uterine segment for premature labor signs:
    a. Contractility
    b. Lower uterine segment ballooning

Any changes on the cervix and/or the lower uterine segment are treated with education, reduced activity and or complete bed rest. If cervical length continues to decline despite bed rest, treatment according to our preterm labor management protocol is instituted.
Such management has for the most part eliminated the complications of such pregnancies with minimal episodes of IUGR, preterm delivery secondary to preterm labor, abruptio, and pre-eclampsia.