A practical approach to the prevention of miscarriage: Part 5 – antiphospholipid syndrome as a cause of spontaneous abortion

J.H. Check, *M.D., Ph.D.*

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ (USA)

Summary

Purpose: To describe the diagnosis and treatment of antiphospholipid syndrome as it relates to spontaneous abortion. *Methods:* The relative importance of performing tests of antiphospholipid antibodies that prolong the partial thromboplastin time and other autoantibodies against phospholipids measured by ELISA are discussed. *Results:* The most important diagnostic tests are the lupus anticoagulant, anticardiolipin antibody and antiphosphatidyl serine. Low molecular weight heparin and low dose aspirin are the two most important therapies. *Conclusions:* Women with recurrent miscarriages or even an unexplained miscarriage especially after ten weeks (but sometimes even early first trimester) or a history of thrombosis or intrauterine growth restriction and maybe preeclampsia are candidates for anticoagulant therapy, especially with the presence of significant levels of the lupus anticoagulant or anticardiolipin or antiphosphatidyl serine antibodies (> 40 pl units/ml).

Key words: Antiphospholipid antibodies; Lupus anticoagulant; Spontaneous abortion; Low molecular weight heparin; Aspirin.

The antiphospholipid antibodies that prolong the phospholipid-dependent clotting assays

Antiphospholipid syndrome (APS) is a well documented cause of miscarriage. APS was first described by Hughes *et al.* as a condition that predisposes a person to arterial and/or venous thrombosis, cerebrovascular disease, and when present in women, a predisposition to spontaneous abortion [1].

APS is associated with antibodies directed against anionic phospholipids or phospholipid containing structures. The original description only referred to those antiphospholipid antibodies that prolong phospholipid-dependent clotting assays, e.g., the lupus anticoagulant where the clotting defect is not corrected with normal plasma but with the addition of phospholipids. The presence of the lupus anticoagulant will cause prolongation of the activated partial thromboplastin time, the diluted Russells' viper venom time, and Kaolin clotting time [1].

Other antiphospholipid antibodies

There are, however, other antiphospholipid antibodies that do not prolong the phospholipid-dependent clotting assays. These include antibodies to cardiolipin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, phosphatidylinositol, and phosphatidic acid, plus B2-glycoprotein I. The detection of these antiphospholipids, not detected in clotting assays, requires enzyme-linked immunosorbent assays (ELISA) using surfaces coated with the particular phospholipids. The measurements are typically in antiphospholipid antibody (aPL) units (1 unit equals the binding capacity of 1 μg/ml of pure phospholipids). A level > 20 GPL U/ml for anticardiolipin antibody IgG is considered weakly positive.

Types of fetal loss associated with antiphospholipid antibodies

Antiphospholipid antibodies have been associated with early spontaneous abortion, late first trimester or mid-trimester spontaneous abortion, pregnancy-induced hypertension, preeclampsia, and intrauterine growth restriction. Different antiphospholipid antibodies have been associated with losses at different stages of pregnancy.

The only antiphospholipid antibodies associated with early first trimester spontaneous abortion is antiphosphatidylethanolamine (aPE) and antiphosphatidylserine (aPS) [2]. These two aPLs may affect cell division during embryogenesis and normal function of the trophoblast [2, 3].

Revised manuscript accepted for publication March 31, 2010

The lupus anticoagulant is only associated with second rather than first trimester spontaneous abortion [4]. Frequently the lupus anticoagulant and anticardiolipin antibody co-exist, however when only the anticardiolipin antibody IgG is detected, the likelihood of live birth is decreased by 36-48% compared to women having neither antiphospholipid antibody [5].

There is conflicting data in the literature as to the relative importance of IgG vs IgM anticardiolipin antibodies. One study suggested that mainly IgG anticardiolipin antibodies predicted spontaneous abortion [6]. However another study found IgM to show a stronger correlation to pregnancy outcome than IgG [5]. An older study found IgM for anticardiolipin to be more common than IgG [7]. I frequently find slightly elevated titers of IgM common with low titers of IgG. I have watched to see if IgG antibodies subsequently become positive but almost always they do not. Thus I have questioned something about the IgM measurement that leads to false positive tests.

Slightly positive IgG and IgM for anticardiolipin are common. However they have doubtful clinical significance and probably do not confer any greater risk of miscarriage to a woman with low positive levels [8]. Though titers above 20 are considered positive, real clinical significance may not be found until the titer is > 40 GPL or MPL. One study showed that in women with a previous history of spontaneous abortion 80% will have another fetal loss if the aCL is > 80 CPL [9].

Most commercial laboratories perform anticardiolipin antibodies and antiphosphotidylserine assays. Since one study showed that the trophoblastic layer directly in contact with the maternal circulation is more reactive with antiphosphatidylserine vs anticardiolipin antibodies, I usually screen all women with infertility and those with a history of miscarriage with these two antibodies [10].

I do not believe there are enough data to support positive antiphosphatidylethanolamine antibodies as a cause of early first trimester miscarriage. Also these antibodies may be a cause of mid to late pregnancy loss related to binding to phosphatidylethanolamine-kininogen complexes which results in thrombin-induced platelet aggregation [3]. Nevertheless, I do not measure this assay routinely as I do anticardiolipin and antiphosphatidylserine antibodies because the antiphosphatidylethanolamine assay level is frequently not paid for by third party carriers. Frequently if aPE is positive so will aCL or aPS. However, I will order this assay for some women with unexplained recurrent miscarriage who tested negative for lupus anticoagulant, aCL or aPS, especially early first trimester losses.

One study showed an increased frequently of antiphosphatidylcholine (aPC), antiphosphatidylglycerol (aPG), phosphatidic acid (aPA) and antiphosphatidyl inositol (aPI) in women with recurrent miscarriage [11]. However I am not aware of any study demonstrating the significance of these antiphospholipid antibies if aCL or aPS are absent as far as predicting miscarriage or the likelihood of them being present in the absence of aPS or aCL.

Caveat – measure for antiphospholipid antibodies when pregnant or near the time of pregnancy loss

Sometimes aCL or aPS are absent or of low titer in the non-pregnant state and exists only to become very positive during the pregnancy [12]. Thus in a woman with a previous history of unexplained spontaneous abortion certainly the lupus anticoagulant, aPS and aCL should be measured even if the woman was previously negative for these factors. These antiphopholipid antibodies should also be measured if there is intrauterine growth restriction or appearance of hypertension while pregnant.

Implantation failure

When a couple fails to conceive after having normal intercourse or intrauterine insemination there is the possibility that the sperm is not fertilizing the egg or there is failure of the conceptus to cleave, or the failure of the embryo to adhere to the endometrium, or early rejection of the embryo after trophoblast invasion. Failure to conceive despite the transfer of cleaved embryos eliminates the first two possibilities. One study suggested that antibodies against cofactor proteins, e.g., prothrombin and annexin V may be associated with failed implantation following embryo transfer [13].

Therapy

The main treatment for pregnancy loss in women with the antiphosphalipid syndrome is either unfractionated heparin or low molecular weight heparin either alone or with low-dose aspirin [14-17].

Determining who needs treatment is more problematic. One study found a live delivery rate of 80% in women with recurrent miscarriage of three or more in a row positive for aPL [18]. In fact in the study by Pattison *et al.* and a study by Cowchock *et al.* aspirin did no better than placebo [19].

Two trials compared aspirin alone vs aspirin and heparin together for recurrent pregnancy loss with positive aPL and the one by Kutteh *et al.* found a 44% live birth rate with aspirin alone vs 80% with heparin and aspirin and in the study by Rai *et al.* a rate of 42% with aspirin vs 71% with the combination [20, 21]. These two studies lacked a placebo control and thus it is not clear that the use of low-dose aspirin would have resulted in any better live delivery rate than placebo.

These two aforementioned studies guided the treatment philosophy from the mid 90s. However, a randomized controlled heparin aspirin trial published in 2009 failed to show any difference in live deliveries in those taking low-dose aspirin alone (79.1%) vs those taking low molecular weight heparin and aspirin together (77.8%) [22]. None of the women had pregnancy-related thrombosis [22]. There were four other studies published in 2000 or later failing to find any improvement of low molecular weight heparin with aspirin vs aspirin alone [23-26].

Since low molecular weight heparin significantly reduces the risk of hemorrhage, osteoporosis, and heparin-induced thrombocytopenia as compared to heparin it makes more sense to use low molecular weight heparin if one chooses to still use this over aspirin alone. The recommended dosage is for enoxaparin 1 mg/kg/day [11]. This is more of a prophylactic dosage. However, for women with a previous history of deep-vein thrombosis the recommendation is to give this dosage every 12 hours [11]. Some even think that this higher dosage should be given to women with late first trimester (> 10 weeks) or mid trimester losses without a history of thrombosis [14, 15, 17, 27]. Evidence exists that low molecular weight heparin is as effective as unfactionated heparin in preventing miscarriage in women with antiphospholipid syndrome [28]. When women are treated with low molecular weight heparin full dosage one cannot monitor the dosage by evaluating prolongation of the partial thromplastin line (PTT) since it does not prolong the PTT.

Therapies other than anticoagulation

Probably in more severe cases anticoagulant therapy does improve the likelihood of a live delivery to 75-80%. Thus there are about 20-25% who do not respond. The possibility exists that in some particular women there is some other unidentified factor causing the miscarriages such that either both factors contributed but only one was corrected by anticoagulant therapy or in this case aPL was a non-factor. Alternatively, the aPL is the sole factor but anticoagulation is not correcting the problem. Of course there is also the possibility that all the previous losses may have been from APS but the last one despite anticoagulation therapy was merely fortuitously related to an accidental aneuploidy, for example. Thus it is imperative to perform a chromosome analysis on the aborted fetus.

Certainly if a chromosomally normal fetus is found and the woman was taking low molecular weight heparin only once per day because of a lack of history of later miscarriage or history of thrombosis the dosage should be increased to twice daily.

As previously mentioned aPL may cause fetal loss in some cases in a manner different than thrombosis [29-33]. Since this could be the reason why in some cases anticoagulation are not effective, other therapies aimed at reducing antibodies or their effects have been tried. These include glucocorticoid therapy and intravenous immunoglobulin (IVIG) therapy. The most recent studies have failed to demonstrate any beneficial effect of glucocorticoids [34-36]. Considering all the side-effects of glucocorticoids this therapy should not be given.

Intravenous immunoglobulin is extremely expensive. There are no data to suggest that it is either more effective or can treat anticoagulant resistant cases of APS [37-39]. There are some preliminary data to suggest that IVIG may be superior to anticoagulants in preventing pre-eclampsia, intrauterine growth restriction and premature births [37-41].

Conclusions and personal thoughts

Enough evidence exists that the antiphospholipid syndrome is a definite entity that can cause fetal loss. It definitely can cause pregnancy losses after ten weeks when the platelets become more thrombophilic. APS probably but not definitely can be the cause of spontaneous abortions in the earlier parts of the first trimester though the supporting evidence is not as clear as later losses. APS is also very likely linked to the aforementioned later obstetric complications.

Most likely the majority of women treated for APS do not really need any therapy. These are generally women with a previous history of at least one miscarriage or even recurrent miscarriage without a history of deep vein thrombosis or previous intrauterine growth restriction with mildly positive aCL < 40 GPL or MPL U/ml who would probably do just as well with placebo.

My personal policy is even though I know that the majority probably do not need therapy, my experience has found that a woman who is slightly positive, i.e., ≥ 20 GPL is more likely than one completely negative to raise this level > 40 during the pregnancy. Nevertheless I repeat measurement for aPL and aPS in all women during their first trimester (I do not see them beyond the first trimester) including women with no prior history of miscarriage but merely infertility. Because of the preciousness of the pregnancy, the treatment in this case is low-dose (81 mg) aspirin.

I have found so many levels of aCL IgM mildly increased with low levels of aCL GPL that never seem to rise even during pregnancy so I do not even give this group low-dose aspirin. Though low-dose aspirin seems benign enough my personal observation is that aspirin is associated with an increased frequency of subchorionic hematomas. Although most of these subchorionic hematomas will resolve, some will expand and dislodge the gestational sac from the endometrial wall causing a miscarriage [42].

Frequently in medicine when a new syndrome is defined the diagnosis and treatment become exaggerated. Since aspirin was found to inhibit thrombosis and thus placental infarcts in women who really have this syndrome, some studies evaluated whether aspirin could increase uterine blood flow even in women without aPL. One study by Wada

et al. did find that low-dose aspirin could increase uterine blood blow [43]. This fact, plus the fact that antiphospholipid antibodies may become positive in women during pregnancy has led some physicians to empirically place women with a history of previous spontaneous abortions or even women failing to conceive despite embryo transfer on low-dose aspirin.

However, our own study of women having frozen thawed embryo transfers failed to confirm Wada *et al.*'s conclusions that low-dose aspirin improves blood flow when given on a daily basis [44]. More importantly we found a significantly lower pregnancy rate in those treated with aspirin [44]. Furthermore in women trying to conceive naturally aspirin by its inhibitory effects on prostaglandins may inhibit the release of the oocyte from the follicle and thus cause luteinized unruptured follicle syndrome [45]. Thus my policy is to only start the aspirin or low-dose aspirin once a definite diagnosis of pregnancy is made. In cases of positive lupus anticoagulant or aCL or aPS > 40 GPL U/ml or a history of previous spontaneous abortion after ten weeks or history of intrauterine growth restriction or deep vein thrombosis I will start aspirin or low molecular weight heparin with the first positive beta hCG level. I am planning to evaluate antiphosphatidylethanolamine (aPE) in women with unexplained spontaneous abortion prior to ten weeks who are negative for lupus anticoagulant, aCL and aPS to determine how likely this would be present if the other three antiphospholipid antibodies were negative. If aPE was solely positive I would consider aspirin or low molecular weight heparin as soon as a pregnancy is known.

Until the very recent study by Laskin *et al.* I was of the belief that low molecular weight heparin (LMWH) was superior to aspirin so for legitimate cases I would use low molecular weight heparin and reserve aspirin for the milder cases [22]. Frequently I used the LMWH alone once daily but for more severe cases either add aspirin or use LMWH twice daily. I have to admit the Laskin *et al.* study has me rethinking the use of low-dose aspirin instead of LMWH.

Though I usually only follow the women through the first trimester usually LMWH would be stopped at 36 weeks because it takes longer for its anticoagulation effect to dissipate than unfractionated heparin. The woman is genereally switched to unfractionated heparin at this point for fear of an epidural hematoma or emergency C-section [27]. Low-dose aspirin is stopped at 34 weeks because prostaglandins are needed to close the ductus arteriosus. If needed the woman could be given unfractionated heparin at this point.

As far as implantation failure following embryo transfer I plan on evaluating further antiannexin V antibodies. I cannot remember the source but there had been a suggestion that unfractionated heparin but not LMWH or aspirin started from the day after retrieval or from the start of the cycle may help if in fact it is proven that these co-factor antibodies really do prevent implantation.

References

[1] Hughes G.R.: "Thrombosis, abortion, cerebral disease, and the lupus anticoagulant". *BMJ*, 1983, *287*, 1088.
[2] McIntyre J.A.: "Antiphospholipid antibodies in implantation failures". *Am. J. Reprod. Immunol.*, 2003, *49*, 221.
[3] Sugi T., Matsubayashi H., Inomo A., Dan L., Makino T.: "Antiphosphatidylethanolamine antibodies in recurrent early pregnancy loss and mid-to-late pregnancy loss". *J. Obstet. Gynaecol. Res.*, 2004, *30*, 326.
[4] Carp H.J., Menashe Y., Frenkel Y., Many A., Nebel L., Toder V., Mashiach S.: "Lupus anticoagulant. Significance in habitual first trimester abortion". *J. Reprod. Med.*, 1993, *38*, 549.
[5] Nielsen H.S., Christiansen O.B.: "Prognostic impact of anticardiolipin antibodies in women with recurrent miscarriage negative for the lupus anticoagulant". *Hum. Reprod.*, 2005, *20*, 1720.
[6] Kaider A.S., Kaider B.D., Janowicz P.B., Roussev R.G.: "Immunodiagnostic evaluation in women with reproductive failures". *Am. J. Reprod. Immunol.*, 1999, *42*, 335.
[7] Matzner W., Chong P., Xu G., Ching W.: "Characterization of antiphospholipid antibodies in women with recurrent spontaneous abortion". *J. Reprod. Med.*, 1994, *39*, 27.
[8] Silver R.M., Porter T.F., van Leeuween I., Jeng G., Scott J.R., Brarch D.W.: "Anticardiolipin antibodies: clinical consequences of 'low titers'". *Obstet. Gynecol.*, 1996, *87*, 494.
[9] Reece E.A., Garofalo J., Zheng X.Z., Assimakopulos E.: "Pregnancy outcome. Influence of antiphospholipid antibody titer, prior pregnancy losses and treatment". *J. Reprod. Med.*, 1997, *42*, 49.
[10] Lyden T.W., Vogt E., Ng A.K., Johnson P.M., Rote N.S.: "Monoclonal antiphospholipid antibody reactivity against human placental trophoblast". *J. Reprod. Immunol.*, 1992, *22*, 1.
[11] Franklin R.D., Kutteh W.H.: "Antiphospholipid antibodies (APA) and recurrent pregnancy loss: treating a unique APA positive population". *Hum. Reprod.*, 2002, *17*, 2981.
[12] Ruiz J.E., Cubillos J., Mendoza J.C., Espinel F.J., Kwak J.Y., Beer A.E.: "Autoantibodies to phospholipids and nuclear antigens in non-pregnant and pregnant Colombian women with recurrent spontaneous abortions". *J. Reprod. Immunol.*, 1995, *28*, 41.
[13] Bizzaro N., Tonutti E., Vilalta D., Tampoia M., Tozzoli R.: "Prevalence and clinical correlation of anti-phospholipid-binding protein antibodies in anticardiolipin-negative patients with systemic lupus erythematosus and women with unexplained recurrent miscarriages". *Arch. Pathol. Lab. Med.*, 2005, *129*, 61.
[14] Branch D.W., Khamashta M.A.: "Antiphospholipid syndrome: obstetric diagnosis, management, and controversies". *Obstet. Gynecol.*, 2003, *101*, 1333.
[15] Derksen R.H., Khamashta M.A., Branch D.W.: "Management of the obstetric antiphospholipid syndrome". *Arthritis. Rheum.*, 2004, *50*, 1028.
[16] Tincani A., Branch W., Levy R.A., Piette J.C, Carp H., Rai R.S. *et al.*: "Treatment of pregnant patients with antiphospholipid syndrome". *Lupus*, 2003, *12*, 524.
[17] Lassere M., Empson M.: "Treatment of antiphospholipid syndrome in pregnancy – a systematic review of randomized therapeutic trials". *Thromb. Res.*, 2004, *114*, 419.
[18] Pattison N.S., Chamley L.W., Birdall M., Zanderigo A.M., Liddell H.S., McDougall J. *et al.*: "Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial". *Am. J. Obstet. Gynecol.*, 2000, *183*, 1008.

[19] Cowchock S., Reece E.A.: "Do low risk pregnant women with antiphospholipid antibodies need to be treated? Organising Group of the Antiphospholipid Treatment Trial". *Am. J. Obstet. Gynecol.*, 1997, *176*, 1099.
[20] Kuttch W.H.: "Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone". *Am. J. Obstet. Gynecol.*, 1996, *174*, 1584.
[21] Rai R., Cohen H., Dave M., Regan L.: "Randomized controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipids antibodies". *BMJ*, 1997, *314*, 253.
[22] Laskin C.A., Spitzer K.A., Clark C.A., Crowther M.R., Ginsberg J.S., Hawker G.A. *et al.*: "Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial". *J. Rheumatol.*, 2009, *36*, 279.
[23] Pattison N.S., Chamley L.W., Birdsall M.: "Does aspirin have a role in improving pregnancy outcome for women with antiphospholipid antibody syndrome – A randomized clinical trial". *Am. J. Obstet. Gynecol.*, 2000, *183*, 1008.
[24] Farquharson R.C., Quenby S., Greaves M.: "Antiphospholipid syndrome in pregnancy: A randomized controlled trial of treatment". *Obstet. Gynecol.*, 2002, *100*, 408.
[25] Jaffe R., Jauniaux E., Hustin J.: "Maternal circulation in the first trimester human placenta-myth or reality?". *Am. J. Obstet. Gynecol.*, 1997, *176*, 695.
[26] Carmona F., Font J., Azulay M., Creus M., Fabregues F., Cervera R. *et al.*: "Risk factors associated with fetal losses in treated antiphospholipid syndrome pregnancies: a multivariate analysis". *Am. J. Reprod. Immunol.*, 2001, *46*, 274.
[27] Empson M., Lassere M., Craig J.C., Scott J.R.: "Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic, trials". *Obstet. Gynecol.*, 2002, *99*, 135.
[28] Stephenson M.D., Ballem P.J., Tsang P., Purkiss S., Ensworth S., Houlihan E., Ensom N.H.: "Treatment of antiphospholipid antibody syndrome (APS) in pregnancy: a randomized pilot trial comparing low molecular weight heparin to unfractionated heparin". J. *Obstet. Gynaecol. Can.*, 2004, *26*, 729.
[29] Philipp T., Kalousek D.K.: "Transcervical embryoscopy in missed abortion". *J. Assist. Reprod. Genet.*, 2001, *18*, 285.
[30] Ogasawara M., Aoki K., Okada S., Suzumori K.: "Embryonic karyotype of abortuses in relation to the number of previous miscarriages". *Fertil. Steril.*, 2000, *73*, 300.
[31] Takakuwa K., Asano K., Arakawa M. Yasuda M., Hasegawa I., Tanaka K.: "Chromosome analysis of aborted conceptuses of recurrent aborters positive for anticardiolipin antibody". *Fertil. Steril.*, 1997, *68*, 54.
[32] Galli M., Barbui T.: "Antiphosopholipid antibodies and pregnancy". *Best. Pract. Res. Clin. Haematol.*, 2003, *16*, 211.
[33] Takeshita Y., Tsurumi Y., Touma S. *et al.*: "Successful delivery in a pregnant woman with lupus anticoagulant positive systemic lupus erythematosus treated with double filtration plasmapheresis". *Ther. Apher.*, 2001, *5*, 22.
[34] Lockshin M.D., Druzin M.L., Qamar T.: "Prednisone does not prevent recurrent fetal death in women with antiphospholipid antibody". *Am. J. Obstet. Gynecol.*, 1989, *160*, 439.
[35] Laskin C.A., Bombardier C., Hannah M.E., Mandel F.P., Ritchle J.W., Farewell V. *et al.*: "Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss". *N. Engl. J. Med.*, 1997, *337*, 148.
[36] Silver R.K., MacGregor Sholl J.S., Hobart J.M., Neerhof M.G., Ragin A.: "Comparative trial of prednisone plus aspirin versus aspirin alone in the treatment of anticardiolipin antibody-positive obstetric patients". *Am. J. Obstet. Gynecol.*, 1993, *169*, 1411.
[37] Spinnato J.A., Clark A.L., Pierangeli S.S., Harris E.N.: "Intravenous immunoglobulin therapy for the antiphospholipid syndrome in pregnancy". *Am. J. Obstet. Gynecol.*, 1995, *172*, 690.
[38] Branch D.W., Peaceman A.M., Druzin M., Silver R.K., El-Sayed Y., Silver R.M. *et al.*: "A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy". *Am. J. Obstet. Gynecol.*, 2000, *182*, 122.
[39] Vaquero E., Lazzarin N., Valensise H., Menghini S., DiPierro G., Cesa F., Romanini C.: "Pregnancy outcome in recurrent spontaneous abortion associated with antiphospholipid antibodies: a comparative study of intravenous immunoglobulin versus prednisone plus low-dose aspirin". *Am. J. Reprod. Immunol.*, 2001, *45*, 174.
[40] Harris E.N., Pierangeli S.S.: "Utilization of intravenous immunoglobulin therapy to treat recurrent pregnancy loss in the antiphospholipid syndrome: a review". *Scant. J. Rheumatol.*, 1998, *107* (suppl.), 97.
[41] Valensie H., Vaquero E., De Carolis C.: "Normal fetal growth in women with antiphospholipid syndrome treated with high dose intravenous immunoglobulin (IVIG)". *Prenat. Diagn.*, 1995t, *15*, 509.
[42] Kwak J.Y., Quality E.A., Gilman Sachs A., Beaman K.D., Beer A.E.: "Intravenous immunoglobulin infusion therapy in women with recurrent spontaneous abortions of immune etiologies". *J. Reprod. Immunol.*, 1995, *28*, 175.
[43] Wada I., Hsu C.C., Williams G., Macnamee M.C., Brinsden P.R.: "The benefits of low-dose aspirin therapy in women with impaired uterine perfusion during assisted conception". *Hum. Reprod.*, 1994, *9*, 1954.
[44] Check J.H., Dietterich C., Lurie D., Nazari A., Chuong J.: "A matched study to determine whether low-dose aspirin without heparin improves pregnancy rates following frozen embryo transfer and/or affects endometrial sonographic parameters". *J. Assist. Reprod. Genet.*, 1998, *15*, 579.
[45] Check J.H., Dietterich C., Nowroozi K., Wu C.H.: "Comparison of various therapies for the luteinized unruptured follicle (LUF) syndrome". *Int. J. Fertil.*, 1992, *37*, 33.

Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com