Korean Society of Maternal Fetal Medicine
Vol. 7 No. 1 March 2011

반복유산환자에서 임신 중 정맥 내 면역글로불린 치료와 전자간증의 유병률

관동대학교 의과대학 제일병원 산부인과

안현경 · 양광문 · 이시원 · 김민형 · 정진훈 · 최준식 · 한정열
김문영 · 류현미 · 양재혁 · 최규홍

Prevalence of Preeclampsia Is Not Increased in Women with Recurrent Spontaneous Abortion who Received Intravenous Immunoglobulin G during Pregnancy

Hyun Kyoung Ahn, M.D., Kwang Moon Yang, M.D., Si Won Lee, M.D., Min Hyoung Kim, M.D., Jin Hun Jung, M.D., June Sik Choi, M.D., Jung Yeol Han, M.D., Moon Young Kim, M.D., Hyun Mee Rheu, M.D., Jae Hyuk Yang, M.D., Kyu Hong Choi, M.D.

Department of Obstetrics and Gynecology, Cheil General Hospital & Women's Healthcare Center, Kwandong University College of Medicine, Seoul, Korea

Objectives: The risk of preeclampsia (PE) has been reported to be increased in women with a history of recurrent spontaneous abortion (RSA). In this study, we aimed to investigate prevalence and clinical characteristics of PE in women with RSA while on intravenous immunoglobulin G (IVIG).

Methods: Women with 2 or more consecutive RSA and elevated peripheral blood CD3-/CD56+ NK cells (>15%) comprised the study group. IVIG treatment (400 mg/kg) was given every 4 weeks starting 5 weeks gestation to 20 weeks gestation. Controls were age and parity matched healthy women without a history of RSA and delivered a live born infant during the same study period. Obstetrical outcome sand complications were compared between the study group and controls.

Results: PE occurred in 4 of 228 deliveries (1.75%) and this is the comparable to controls (9/456, 2.0%). The birth weight of study group (3295.6±486.4 gm) and controls (3246.1±482.0 gm), and length of gestation of study group (39.0±1.6 wks) and controls (38.9±1.5 wks) were not different. The incidences of gestational diabetes (6.5 vs. 4.8%), preterm birth (6.6% vs. 7.5%), IUGR (4.8 vs. 6.2%), and NICU admission (9.6 vs. 9.6%) were not different between the study group and controls.

Conclusion: Prevalence of PE in women with RSA who were treated with IVIG is not increased when compared to that of general population.

Key words: Recurrent spontaneous abortion (RSA), Preeclmpsia (PE), Intravenous immunoglobulin (IVIG), Immune etiology

Recurrent spontaneous abortion (RSA) is a main issue for women's health, with 3 or more successive losses affecting 1% to 2% of women of reproductive age and 2 or more successive losses affecting approximately 5%.[1] Multiple etiologies for RSA have been reported including chromosomal-6%, anatomic-1%, hormonal-5%, immunologic-65%, and unexplained-23%.[2] In a recent study of Ford and Schust et al., approximately 20% of women with RSA have autoimmune etiologies and 50% of them were reported to be unknown including non-anti-phospholipid

접수일 : 2011. 3. 15.
주관책임자 : 안현경
E-mail : sun3rd@hanmail.net

antibody-related thrombophilic tendencies.[3] Therefore, approximately 65-70% of RSA can be related to immunological etiologies. Kwak-Kim et al. reported that 37.1% of women with RSA have elevated peripheral blood natural killer (NK) cells.[4] In addition, women with RSA have significantly elevated Th1/Th2 cytokine-producing cell ratios in the peripheral blood when compared to normal controls.[5] Therefore, local and systemic inflammatory processes and coagulation seem to play a major role in RSA.

Preeclampsia (PE) is a pregnancy-specific syndrome that carries high risk of perinatal and maternal mortality and morbidity. PE is commonly understood as a hypertensive disorder of pregnancy characterized by increased blood pressure (gestational blood pressure elevation) and accompanied proteinuria, both occurring after 20 weeks gestation.[6] Despite the large amount of researches focused on PE, patho-physiological causes of PE remain uncertain.

Previous studies suggest that in preeclamptic women, abnormal cytotrophoblast invasion of maternal spiral arteries in the endometrium leads to improper remodeling of uterine spiral arteries and placental hypoxia.[7] These changes were reported to induce intrauterine hypoxemia, placental apoptosis and release of placental debris. Circulation of the cellular debris, or some as yet unidentified vascular factors, is thought to lead to the generalized vascular endothelial activation that is recognized as the syndrome of PE.[8] There is yet no agreement on the mechanisms that underlie this event. A possible explanation may be immune mal-adaptation.[9]

Recently, altered immune responses have been suggested to be involved in pathogenesis of PE, which may concern inflammatory context of this disease.[10] One of the most interesting directions in contemporary research on PE pertains to the rather unexpected beneficial role of the innate immune system, so-called 'natural killer (NK) cells', which play in the healthy progression of a normal pregnancy. Increasing evidence supports a fundamental dependence on sufficient NK cell activation in order for adequate placentation to occur.[11] IVIG is used in recurrent spontaneous abortion, especially in immunologic abortion case. Even though some studies have failed to confirm the beneficial effect,[12,13] many studies have shown that IVIG therapy is safe and effective for women with immunologic abortion.[14,15] IVIG may protect the embryo through several mechanisms: suppression of activated natural killer (NK) cells, deactivation of T cells and polyclonal B cells, control of harmful antibodies through the action of anti-idiotype antibodies and shift from a Th1 to Th2 bias.[16] In addition, intravenous gamma globulin may provide a protective CD200 signal, an important defence molecule that may play a variety of roles including promoting activation of T-regulatory cells which are often deficient in patients who have complication of pregnancy.[17,18]

Trogstad et al. reported that the risk of PE increased in women who have both been treated for infertility and experienced recurrent miscarriage.[19] These results are compatible with the idea that infertility, recurrent miscarriage and PE may share elements of the same etiology. PE, growth restriction, recurrent abortion, and preterm birth in many cases are caused by abnormal implantation with failure of this process.[20]

In this study, we aimed to investigate prevalence and clinical characteristics of PE in women with RSA while on anti-inflammatory and anti-coagulation treatment. For the purpose of verify the effect of immune modulation treatment to prevalence and clinical characteristics of PE, we retrospectively analyzes whether treatment of immunologic abortion with IVIG reduce the other pregnancy complications supposed to continuum with the same cause of RSA.

MATERIALS AND METHODS

We performed a retrospective study involving members of Cheil general hospital. Two hundred twenty eight pregnancies in patients with a history of recurrent spontaneous abortion and treated with IVIG were retrospectively evaluated. This population had been screened with a battery of immunologic test, including antiphospholipid antibody, antimicrosomal antibody, antithyroglobulin antibody, antinuclear antibody. CD4 and CD8 T cell counts and $CD3^-/CD56^+$ natural killer cell levels had been determined by flow cytometry. And abnormal result on $CD3^-/CD56^+$ NK cells (>15%) had been detected, so they were treated with IVIG. IVIG

treatment (400 mg/kg) was given every 4 weeks starting 5 weeks gestation to 20 weeks gestation. Controls were age and parity matched healthy women without a history of RSA and delivered a live born infant during the same study period. Regarding maternal outcome, PE, gestational diabetes mellitus, time of delivery were compared between study group and control group. Neonatal outcome included weight at birth, Apgar score at 1 and 5 minutes, and congenital malformation. Intrauterine growth retardation (IUGR) was considered if the baby's birth weight below the 10th percentile for gestational age. PE and gestational diabetes were defined as previously reported.[21,22] Deliveries before 37 completed weeks were considered preterm. Admissions to neonatal intensive care units (NICUs) were also evaluated. All statistical analysis was carried out using the SPSS statistical package for Windows. Discrete variables were compared using χ^2-test or Fisher's exact test, as appropriate. Continuous variables were compared using and Student's *t*-test.

RESULTS

There were 228 women who had recurrent spontaneous abortion and 456 controls.

Table 1 shows the characteristics of the patients. No significant differences were noted between the 2 groups concerning age. A significant difference was found in mean gravidity between groups (4.1±1.4 in study group compared with 2.1±1.3 in control group). The mean parity was 0.36 in both groups.

Table 2 demonstrates the pregnancy outcomes in the two groups. The mean gestational ages were 39.0 weeks in the study group and 39.1 weeks in the control group. The mean weight of the newborns was 3,296 g in the study group and 3,246 g in the control group. No significant differences were found in the APGAR score at 1 minute and 5 minutes between two groups (8.1 vs. 8.1 at 1 minutes, 9.0 vs. 9.1 at 5 minutes). The incidence of preterm deliveries was 6.6% (15 out of 228) in the study group compared with 7.5% (34 out of 456) in the control group. The frequency of IUGR was similar in the study group compared with control group (4.82% vs. 6.29%). The frequency of PE and gestational diabetes mellitus were similar in the study group compared with the control group (1.75% vs. 2.0%; 6.5% vs.

Table 1. Baseline characteristics of the women in the study groups

Characteristics	IVIG group	Control group
Mean age (years)	33.1±3.3	33.4±3.2
Gravidity	4.12±1.4	2.1±1.3
Parity	0.4±0.5	0.4±0.5

Values are given as mean±SD.

Table 2. Major outcome of pregnancy in the study groups

Outcome	IVIG group	Control group	*P*-values
Birth weight (g±SD)	3,296±486	3,246±482	0.69
Mean APGAR score at 1 minute (±SD)	8.1±0.8	8.2±0.8	0.77
Mean APGAR score at 5 minutes (±SD)	8.96±0.6	9.05±0.6	0.87
Mean delivery weeks (±SD)	39.04±1.6	39.09±1.5	0.52
Preterm labor	15 (6.57%)	34 (7.45%)	0.4
Growth retardation	11 (4.82%)	27 (6.29%)	0.3
Preeclampsia	4 (1.75%)	9 (2.0%)	0.6
Gestational diabetes mellitus	15 (6.6%)	22 (4.82%)	0.2
NICU admission	22 (9.6%)	44 (15.7%)	0.5
Anomaly of newborn	3 (1.3%)	2 (0.4%)	0.2

4.8%). The NICU admission rate of newborn was 9.6% in the study group compared with 15.0% in the control group. Three newborns in study group had congenital malformations (1.3%), one poly-syndactyly, one ventricular septal defect, and one horseshoe kidney. Two newborn in control group had congenital malformations (0.4%), one cleft palate and one cleft lip and palate.

DISCUSSION

Placenta mediated pregnancy complication including PE, abruptio placenta, intrauterine growth restriction and pregnancy loss are among the leading causes of maternal and neonatal morbidity and mortality. Placenta mediated pregnancy complications can result in devastating pregnancy outcomes and are not infrequent. The causes of placenta mediated pregnancy complications remains largely unknown but are thought to, at least in part, share a common theme of activated hemostasis at the placental interface, which may result in placental vessel thrombosis and abnormal placental development.

The risk of PE appears to be increased in women with a history of RSA. Recently, altered immune responses have been suspected to be involved in PE pathogenesis, which may concern the inflammatory context in which an immune response is mounted. Unfavorable immune responses to fetus and/or placenta could yield not only PE, but a wide range of obstetrical complications including RSA, and intra IUGR by the mechanisms of placental inflammation and thrombosis.

NK cells accumulate during early pregnancy in the area of implantation and accompany invading trophoblasts.[23] uNK cells may also play a pivotal role in angiogenesis and artery remodelling at the feto-maternal interface.[24,25] uNK cells act by means of secreting trophoblast invasion-promoting cytokines (IL-8 and IP-10) in addition to angiogenic factors such as VEGF and PIGF. This combination of cytokines and angiogenic factors serves to induce and support the invasion of the tumor like extravillous trophoblasts into the maternal spiral arteries in order to achieve the remodeling of the spiral arterioles required for adequate placental perfusion later in the pregnancy. It has been suggested that uNK cells could contribute to the development of PE by inducing the lysis of trophoblast cells lacking HLA-G since it could interfere an invasion of the trophoblast cells and hamper sufficient supply of oxygen and nutrients to the developing placenta.[26,27] Therefore, the disease of PE results from insufficient activation of the uNK cells which prematurely halts the process of placental development and maternal decidual spiral artery remodeling by the extravillous cytotrophoblasts. Alteration of NK cell function may be important in failure to reorganize blood vessels at the maternal-fetal interface and account in part for PE.[28] The pre-eclamptic state also seems to entail a dominance of activity among the peripheral ($CD56^{dim}$ dominant) NK cells whose increased activity has been associated not only with PE, but recurrent spontaneous abortions and infertility.[29,30]

It has been reported that the percentages αβ-receptor positive CD8+T cells as well as classical $CD16^{+}/56^{+}$ NK cells in relation to $CD45^{+}$ cells were significantly lower in the deciduas of preeclamptic patients than those of controls.[31] Similarly, a significant reduction of $CD8^{+}$ and of $CD56^{+}$ lymphocytes in the decidua of preeclamptic patients by using immuno-histochemistry has been reported.[32] This observation is rather surprising, since inflammation is thought to be an important component of clinical manifestation of PE.[33,34] Contrarily, a significant increase in $CD8^{+}$ decidual T cells by immuno-histochemistry and an increased percentage of both $CD8^{+}/CD28^{+}$ and $CD16^{+}/CD56^{+}$cells by FACS analysis have been reported in patients with PE.[35,36] Discrepancies in these studies may be partially explained by overall number of the cell populations vs. ratio of specific population againt total lymphocyte counts ($CD45^{+}$ cells).[36] The number of $CD16^{-}/CD56^{+}$uNK cells were not different in PE and controls.[31] PE was associated with an increased number of $CD\ 56^{dim}$ NK cells in umbilical cord blood compared to controls.[37] Thus, aberrant NK cell activity may have a significant role in the pathogenesis of PE. NK cells may act toward the developing fetus as either friend or foe depending on which sub-population (peripheral or uterine/decidual) predominates.

IVIG has numerous immuno-modulatory actions. It inhibits production of pro-inflammatory cytokines, such as IL-2, TNF-α and INF-γ, and enhances the proportion of cells producing anti-inflammatory cytokines. In addition, IVIG reduces the number and killing activity of peripheral blood NK cells.[38] IVIG may inhibit the action of pathological antibodies by either the interaction of the Fc portion of immunoglobulin with Fc receptors or the Fab receptors,[39] or by passively acting as anti-idiotypic antibodies.[40] IVIG modulates the activation and effector function of T and B lymphocytes,[41] neutralizes pathogenic autoantibodies,[42] and interferes with antigen presentation.[43] The anti-inflammatory effect of IVIG may be due to interaction with the complement system.[44] Although a debate regarding the use of IVIG use in treatment of RSA has been presented, it is widely used in the management of autoimmune or alloimmune caused RSA and has been shown to have efficacy resulting in an improved live birth rate in women with immune etiology RSA.[45,46] The risk of PE appears to be especially increased in women who have experienced recurrent miscarriage.[47] Women who have recurrent pregnancy losses are at increased risk for preterm delivery.[48-52] But, in our present study, we have found there is no difference of pregnancy outcome between RSA group with IVIG treatment and normal control group.

In conclusion, according to our present data, prevalence of PE in women with RSA who were treated with anti-inflammatory medications is not increased when compared to that of general population. This support the notion of immune etiology in PE and further investigation is needed to explore the potential therapeutic role of IVIG in PE.

REFERENCES

1. Younis JS, Ohel G, Brenner B, Ben-Ami M. Familial thrombophilia-the scientific rationale for thrombophylaxis in recurrent pregnancy loss? Hum Reprod 1997; 12: 1389-90.
2. Coulam CB. Epidemiology of recurrent spontaneous abortion. Am J Reprod Immunol 1991; 26: 23-7.
3. Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. Rev Obstet Gynecol 2009; 2: 76-83.
4. Kwak JY, Beaman KD, Gilman-Sachs A, Ruiz JE, Schewitz D, Beer AE. Up-regulated expression of CD56+, CD56+/CD16+, and CD19+ cells in peripheral blood lymphocytes in pregnant women with recurrent pregnancy losses. Am J Reprod Immunol 1995; 34: 93-9.
5. Kwak-Kim JY, Chung-Bang HS, Ng SC, Ntrivalas EI, Mangubat CP, Beaman KD, et al. Increased T helper 1 cytokine responses by circulating T cells are present in women with recurrent pregnancy losses and in infertile women with multiple implantation failures after IVF. Hum Reprod 2003; 18: 767-73.
6. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183: S1-22.
7. Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RA. Pathophysiology of preeclampsia: linking placental ischemia/hypoxia with microvascular dysfunction. Microcirculation 2002; 9: 147-60.
8. Redman CW, Sargent IL. Placental debris, oxidative stress and pre-eclampsia. Placenta 2000; 21: 597-602.
9. Redman CW. Immunology of preeclampsia. Semin Perinatol 1991; 15: 257-62.
10. Saito S, Shiozaki A, Nakashima A, Sakai M, Sasaki Y. The role of the immune system in preeclampsia. Mol Aspects Med 2007; 28: 192-209.
11. Sargent IL, Borzychowski AM, Redman CW. NK cells and pre-eclampsia. J Reprod Immunol 2007; 76: 40-4.
12. Mecacci F, Parretti E, Cioni R, Lucchetti R, Magrini A, La Torre P, et al. Thyroid autoimmunity and its association withnon-organ-specific antibodies and subclinical alterations of thyroid function in women with a history of pregnancy loss or preeclampsia. J Reprod Immunol 2000; 46: 39-50.
13. Hill JA, Polgar K, Anderson DJ. T-helper 1-type immunity to trophoblast in women with recurrent spontaneous abortion. JAMA 1995; 273: 1933-6.
14. Stricker RB, Steinleitner A, Bookoff CN, Weckstein LN, Winger EE. Successful treatment of immunologic abortion with low-dose intravenous immunoglobulin. Fertil Steril 2000; 73: 536-40.
15. Sher G, Zouves C, Feinman M, Maassarani G, Matzner W, Chong P, et al. A rational basis for the use of combined heparin/aspirin and IVIG immunotherapy in the treatment of recurrent IVF failure associated with antiphospholipid antibodies. Am J Reprod Immunol 1998; 39: 391-4.
16. Omwandho CO, Gruessner SE, Roberts TK, Tinneberg HR. Intravenous immunoglobulin (IVIG): modes of action in the clinical management of recurrent pregnancy loss (RPL) and selected autoimmune disorders. Clin Chem Lab Med 2004; 42: 359-70.
17. Guerin LR, Prins JR, Robertson SA. Regulatory T-cells and immune tolerance in pregnancy: a new target for infertility treatment? Hum Reprod Update 2009; 15: 517-35.
18. Saito S, Shima T, Nakashima A, Shiozaki A, Ito M, Sasaki Y. What is the role of regulatory T cells in the success of implantation and early pregnancy? J Assist Reprod Genet 2007; 24: 379-86.
19. Trogstad L, Magnus P, Moffett A, Stoltenberg C. The effect of recurrent miscarriage and infertility on the risk of pre-eclampsia. BJOG 2009; 116: 108-13.
20. Roberts JM, Von Versen-Hoeynck F. Maternal fetal/placental interactions and abnormal pregnancy outcomes. Hypertension 2007; 49: 15-6.

21. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. Am J Obstet Gynecol 1988; 158: 892-8.
22. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982; 144: 768-73.
23. Trundley A, Moffett A. Human uterine leukocytes and pregnancy. Tissue Antigens 2004; 63: 1-12.
24. Croy BA, He H, Esadeg S, Wei Q, McCartney D, Zhang J, et al. Uterine natural killer cells: insights into their cellular and molecular biology from mouse modelling. Reproduction 2003; 126: 149-60.
25. Hanna J, Goldman-Wohl D, Hamani Y, Avraham I, Greenfield C, Natanson-Yaron S, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med 2006; 12: 1065-74.
26. Hara N, Fujii T, Yamashita T, Kozuma S, Okai T, Taketani Y. Altered expression of human leukocyte antigen G (HLA-G) on extravillous trophoblasts in preeclampsia: immunohistological demonstration with anti-HLA-G specific antibody "87G" and anti-cytokeratin antibody "CAM5.2". Am J Reprod Immunol 1996; 36: 349-58.
27. Goldman-Wohl DS, Ariel I, Greenfield C, Hochner-Celnikier D, Cross J, Fisher S, et al. Lack of human leukocyte antigen-G expression in extravillous trophoblasts is associated with pre-eclampsia. Mol Hum Reprod 2000; 6: 88-95.
28. Sakai M, Ogawa K, Shiozaki A, Yoneda S, Sasaki Y, Nagata K, et al. Serum granulysin is a marker for Th1 type immunity in pre-eclampsia. Clin Exp Immunol 2004; 136: 114-9.
29. Kopcow HD, Karumanchi SA. Angiogenic factors and natural killer (NK) cells in the pathogenesis of preeclampsia. J Reprod Immunol 2007; 76: 23-9.
30. Hiby SE, Regan L, Lo W, Farrell L, Carrington M, Moffett A. Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage. Hum Reprod 2008; 23: 972-6.
31. Rieger L, Segerer S, Bernar T, Kapp M, Majic M, Morr AK, et al. Specific subsets of immune cells in human decidua differ between normal pregnancy and preeclampsia-a prospective observational study. Reprod Biol Endocrinol 2009; 7: 132.
32. Williams PJ, Bulmer JN, Searle RF, Innes BA, Robson SC. Altered decidual leucocyte populations in the placental bed in pre-eclampsia and foetal growth restriction: a comparison with late normal pregnancy. Reproduction 2009; 138: 177-84.
33. Saito S, Sakai M. Th1/Th2 balance in preeclampsia. J Reprod Immunol 2003; 59: 161-73.
34. Redman CW, Sargent IL. Placental stress and pre-eclampsia: a revised view. Placenta 2009; 30 Suppl A: S38-42.
35. Stallmach T, Hebisch G, Orban P, Lu X. Aberrant positioning of trophoblast and lymphocytes in the feto-maternal interface with pre-eclampsia. Virchows Arch 1999; 434: 207-11.
36. Wilczynski JR, Tchorzewski H, Banasik M, Głowacka E, Wieczorek A, Lewkowicz P, et al. Lymphocyte subset distribution and cytokine secretion in third trimester decidua in normal pregnancy and preeclampsia. Eur J Obstet Gynecol Reprod Biol 2003; 109: 8-15.
37. Bujold E, Chaiworapongsa T, Romero R, Gervasi MT, Espinoza J, Goncalves LF, et al. Neonates born to pre-eclamptic mothers have a higher percentage of natural killer cells (CD3-/CD56+16+) in umbilical cord blood than those without pre-eclampsia. J Matern Fetal Neonatal Med 2003; 14: 305-12.
38. Finberg RW, Newburger JW, Mikati MA, Heller AH, Burns JC. Effect of high doses of intravenously administered immune globulin on natural killer cell activity in peripheral blood. J Pediatr 1992; 120: 376-80.
39. Dietrich G, Algiman M, Sultan Y, Nydegger UE, Kazatchkine MD. Origin of anti-idiotypic activity against anti-factor VIII autoantibodies in pools of normal human immunoglobulin G (IVIg). Blood 1992; 79: 2946-51.
40. Dietrich G, Kaveri SV, Kazatchkine MD. A V region-connected autoreactive subfraction of normal human serum immunoglobulin G. Eur J Immunol 1992; 22: 1701-6.
41. Vassilev T, Gelin C, Kaveri SV, Zilber MT, Boumsell L, Kazatchkine MD. Antibodies to the CD5 molecule in normal human immunoglobulins for therapeutic use (intravenous immunoglobulins, IVIg). Clin Exp Immunol 1993; 92: 369-72.
42. Kaveri SV, Dietrich G, Kazatchkine MD. Can intravenous immunoglobulin treatment regulate autoimmune responses? Semin Hematol 1992; 29: 64-71.
43. Fehr J, Hofmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. N Engl J Med 1982; 306: 1254-8.
44. Carp HJ, Sapir T, Shoenfeld Y. Intravenous immunoglobulin and recurrent pregnancy loss. Clin Rev Allergy Immunol 2005; 29: 327-32.
45. Hutton B, Sharma R, Fergusson D, Tinmouth A, Hebert P, Jamieson J, et al. Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review. BJOG 2007; 114: 134-42.
46. Kotlan B, Padanyi A, Batorfi J, Fulop V, Szigetvari I, Rajczy K, et al. Alloimmune and autoimmune background in recurrent pregnancy loss-successful immunotherapy by intravenous immunoglobulin. Am J Reprod Immunol 2006; 55: 331-40.
47. Jablonowska B, Selbing A, Palfi M, Ernerudh J, Kjellberg S, Lindton B. Prevention of recurrent spontaneous abortion by intravenous immunoglobulin: a double-blind placebo-controlled study. Hum Reprod 1999; 14: 838-41.
48. Clifford K, Rai R, Regan L. Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod 1997; 12: 387-9.
49. Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates of and factors associated with recurrence of preterm delivery. Jama 2000; 283: 1591-6.
50. Jivraj S, Anstie B, Cheong YC, Fairlie FM, Laird SM, Li TC. Obstetric and neonatal outcome in women with a history of recurrent miscarriage: a cohort study. Hum Reprod 2001; 16: 102-6.
51. Reginald PW, Beard RW, Chapple J, Forbes PB, Liddell HS, Mowbray JF, et al. Outcome of pregnancies progressing beyond 28 weeks gestation in women with a history of recurrent miscarriage. Br J Obstet Gynaecol 1987; 94: 643-8.
52. Hammoud AO, Merhi ZO, Diamond M, Baumann P. Recurrent pregnancy loss and obstetric outcome. Int J Gynaecol Obstet 2007; 96: 28-9.

「국문초록」

목적: 전자간증은 반복유산의 기왕력이 있는 경우 그 위험성이 증가한다. 본 연구에서는 임신 중 정맥내 면역글로블린 치료를 한 반복유산의 기왕력이 있는 환자에서의 전자간증의 발병율을 보고자하였다.

연구방법: 2회 이상 연속적인 자연유산을 기왕력이 있는 반복유산 환자에서 자연살해세포가 15% 이상 증가한 경우로 정맥내 면역글로불린을 임신초기에 주입받은 군을 환자군으로 정의하였다. 반복유산의 기왕력이 없는 임신부 중 나이 및 분만력을 맞추어 대조군을 선정하여 임신 결과를 환자군과 비교하였다.

결과: 전자간증은 환자군에서 1.75% (4/228) 발병하였으며 대조군에서 2% (9/456) 발병하여 통계적인 차이를 보이지 않았다. 신생아의 몸무게 (3,296 ± 486 vs. 3,246 ± 482 g)와 임신주수 (9.0 ± 1.6 vs. 8.9 ± 1.5 wks) 등도 환자군과 대조군에서 큰 차이를 보이지 않았으며, 임신성당뇨 (6.5 vs. 4.8%), 조산 (6.6% vs. 7.5%), 태아발육지연 (4.8 vs. 6.2%), 신생아 중환아실 입원율 (9.6 vs 9.6%) 등도 환자군과 대조군에서 큰 차이가 없었다.

결론: 반복유산의 기왕력이 있는 환자군에서 임신중 정맥내 면역글로불린의 치료는 일반산모군에 비해 전자간증의 빈도를 증가시키지 않았다.

중심 단어: 반복유산, 전자간증, 정맥 내 면역글로불린, 면역학적 원인