MÆDICA - a Journal of Clinical Medicine

STATE-OF-THE-ART

MAEDICA – a Journal of Clinical Medicine
2013; 8(2): 182-188

Therapeutic Options for Immune Thrombocytopenia (ITP) During Pregnancy

Anca NICOLESCU[a]; Ana Maria VLADAREANU[a]; Irina VOICAN[a]; Minodora ONISAI[a]; Radu VLADAREANU[b]

[a]Emergency University Hospital, Department of Hematology, Bucarest, Romania
[b]Elias Emergency University Hospital, Department of Obstetrics-Gynecology, Bucharest, Romania

ABSTRACT

The incidence of ITP during pregnancy is low. When ITP is suspected it is necessary to perform an extended set of clinical and biological investigations in order to determine the etiology of thrombocytopenia, as the diagnosis of ITP is a process of exclusion, because there is no sensitive and specific diagnostic test so far. The treatment for ITP during pregnancy represents a challenge, being necessary in the cases selected according to the obstetrical indications, to the degree of maternal thrombocytopenia and to the extent of the hemorrhagic syndrome, as well as according to the adverse reactions of the treatment on the mother and fetus.

Keywords: Immune thrombocytopenia, pregnancy, corticotherapy, hemorrhage

GENERAL CONSIDERATION

Primary Immune thrombocytopenia – ITP (idiopathic) – is defined as isolated thrombocytopenia, without a clear etiology, not associated with other causes of thrombocytopenia (1), whereas secondary immune thrombocytopenia has a causing event. In both instances, the etiopathologic mechanism is an immune one, characterized by: the premature increase of the platelet destruction mediated by autoantibodies, the impairment of the intramedullar production and other immune mechanisms mediated by T lymphocyte (T cell) (1). The place of destruction is usually at the level of the reticuloendothelial system of the spleen and very rarely at the level of the liver.

Even nowadays, the diagnosis of ITP is a process of exclusion, as there are no clinical tests or specific, sensitive laboratory method able to detect the membranous autoantibodies or the free plasma antibodies. ITP is characterized by isolated thrombocytopenia, a normal or higher number of bone marrow megakaryocytes and the absence of splenomegaly (2).

The incidence of ITP during pregnancy is estimated at approximately 1%- 1‰ of the pregnant women, representing approximately 3% of the pregnant women with thrombocyto-

Address for correspondence:
Emil G. Haritinian, Foisor Clinical Hospital of Orthopedics, Traumatology and Osteo-Articular Tuberculosis, 35-37 Ferdinand Boulevard, District no. 2, 021308, Bucharest, Romania.
E-mail: haritinian@gmail.com

Article received on the 17th of February 2013. Article accepted on the 11th of June 2013.

penia (3). In most cases, the diagnosis of chronic ITP precedes the pregnancy, but there are cases when ITP can appear de novo during the pregnancy. The most frequently encountered clinical form is the chronic form. ITP during pregnancy presents certain particular aspects which entail multiple risks: obstetrical, hematological and neonatal, and that is why it is necessary to monitor carefully the pregnant woman from the hematological and obstetrical points of view (4,5).

The treatment for ITP during pregnancy is administered after making a complete assessment of the bleeding risk, taking into account primarily the obstetrical criteria. The treatment methods used for classical ITP (4) (corticotherapy, immunosuppression) may produce iatrogenic effects and represent an additional source of complications both for the mother and the fetus.

Women with a history of ITP prior to the pregnancy or in whom an incidental decrease of the platelet count below 70000/mmc is detected are more likely to have ITP than gestational thrombocytopenia (6). A rapid increase of the platelet count after the administration of cortisone or IVIG confirms the immune mechanism of thrombocytopenia. However, the possible causes of secondary immune thrombocytopenia associated with immune diseases, viral infections, HIV infection, antiphospholipid syndrome, etc., must also be taken into consideration. The detection of PAIG (Platelet-Associated Immunoglobulin) in maternal serum does not differentiate clearly between immune thrombocytopenia and gestational thrombocytopenia, since this is neither very sensitive nor specific (7). Once all the other causes of thrombocytopenia have been excluded and there is still a strong suspicion of ITP, the pregnant women must be monitored and treated in accordance with the hematological guidelines, based on a close cooperation between the hematologist and the gynecologist.

The treatment for immune thrombocytopenia during pregnancy is administered after performing clinical and biological investigations, taking into account the etiology of thrombocytopenia, as follows (7):

If the platelet count falls below 50000/mmc, then it is necessary to make a complete assessment of the bleeding risk as against the degree of maternal thrombocytopenia and the gestational age, in order to decide on the necessity of the treatment, to anticipate the manner of delivery, to determine the necessity of epidural anesthesia or the likelihood of the occurrence of maternal or fetal complications (7).

Indication for ITP treatment during pregnancy

It is well known that ITP during pregnancy has a chronic evolution and that the methods of treatment used for classical ITP (corticotherapy, splenectomy, immunosuppression) may generate iatrogenic effects and that is why it represents an additional source of complications both for the mother and for the fetus. The treatment during the pregnancy and perinatally of the patients with ITP represents a medical issue. The problems which arise are related to the determination of the best treatment schedule with the minimum complications for the mother and the fetus, the determination of the time of the therapeutic intervention, the determination of the type of delivery and of the type of anesthesia to be used, the possibility of performing invasive procedures. In the study performed by Webert on a large number of pregnant women with ITP, only 30% of the cases required treatment (8).

The therapeutic attitude in the case of ITP in pregnant women must consider the following principles, taking into account the particular aspects of ITP during pregnancy, the maternal and fetal risks and the adverse reactions of every treatment line on the mother and fetus (5):

- the treatment must be aimed both at the mother and the fetus, while taking into account the fact that the major risks are the fetal ones;
- all the possible adverse reactions in the mother and the fetus must be taken into account, chosing the least harmful option for the fetus, with the clear exclusion of the possibly teratogenic medication;
- initially the aim is to reach remission and to improve the hematological state until delivery, subsequently to reintervene with a more aggressive treatment;
- the treatment requires careful monitoring of the hematological and biochemical parameters and shall be adapted according to the response to the treatment, the degree of adverse reactions to the treatment and the time of the evolution of the pregnancy;

- the treatment lines are similar to those used for ITP in non-pregnant women: corticosteroids, immunoglobulins, splenectomy, immunosuppressants, but with some observations regarding every treatment line. The last generation drugs used for ITP – thrombopoietin analogues (Revolade, Nplate) are not indicated during pregnancy and so far only clinical studies on animals have been performed.

The therapeutic options are wide enough and include first line drugs, second line drugs in the case of refractory ITP, surgical procedures – splenectomy (in selected cases) (10). The treatment for ITP in pregnant women has certain peculiarities as against the general treatment for ITP. The treatment for ITP in pregnant women has a high response rate, but the studies have not shown an improvement of the fetal prognosis.

1. Conservative Measures

It is recommended to refrain from administering specific treatment in the cases in which the platelet count exceeds the value of 50000/mmc or in the case of asymptomatic forms with the platelet count 30000-50000/mmc during the first trimester. Periodical hematological monitoring is recommended (every 2-4 weeks) (3, 10).

2. First line of treatment: Immunoglobulins and/or Corticosteroids

Imnunoglobulins (IVIg) – at present, they are recommended as the first line of treatment during pregnancy.

Mechanism of action – IVIg acts by blocking the FCγ receptors of the macrophages which recognise the autoantibodies linked at the level of the platelets, with their consecutive destruction at the level of the spleen. The latest data reveal that IVIg have also a second function: they activate the FC inhibitory receptor at the level of the macrophages.

Treatment indication. They were initially used as second-line medication, but at present they have been imposed as the first line of treatment. Intavenous immunoglobulins can be administered during the prenatal and perinatal period and especially in case of a lack of response to corticotherapy or if the mother requires very high doses of cortisone. Intravenous immunoglobulins are especially useful in the cases which require the rapid increase of the platelet count, the preoperative preparation of the pregnant woman for any kind of surgery, active hemorrhagic syndrome, the cases of cortisone-resistant ITP or those which associate contraindications for the administration of corticotherapy. They are also recommended when the necessity of corticotherapy is very high in order to maintain a therapeutic response: when it is necessary to administer treatment with Prednisone in a dose of over 30mg/day in order to maintain the platelet count over 30000/mmc (11). In general, the therapeutic administration is preferred to the prophylactic administration, as close as possible to the term of delivery. They have a transitory effect and multiple cycles of treatment may be necessary, associating high costs.

Treatment schedule. Polyvalent immunoglobulins of the IgG type (IVIG type IgG) are used (Octagam) following the schedules: 400 mg/kg body – 5 days or 1g/kg body – 2 days, the courses can be repeated after 2 weeks. The therapeutic response appears rapidly within 12-48 hours, but it does not last (in general it is maintained for a period of maximum 3-4 weeks). The maximum efficiency of the treatment appears after 3-4 courses (5,10). Approximately 70% of the case of corticoresistant ITP responds to the administration of immunoglobulins.

The disadvantages and adverse reactions of IVIg are: the high cost, the development of resistance to treatment in the case of repeated administrations (probably due to the up-regulation phenomenon of the Fc receptors), and occasionally allergic reactions (possibly severe allergic reactions leading to anaphylactic shock, hypersensitivity) (10).

Anti-D immunoglobulins represent an alternative to the use of intravenous immunoglobulins of the IgG type, having a lower cost. Rho (D) immune globulins induce the RE blocking in Rh-positive persons. The mean administered dose is 1.2 mg (it can be administered rapidly, in a few minutes). Benefits: easy administration, accessible cost, more rapid administration. Disadvantages: slower action than IGIv IgG (approximately 72h), they can cause hemolytic anemia and induce tolerance. The safety and degree of efficacy have not been determined in the case of IgG anti-D iv (11). In some centres Iglv anti D have been successfully used – the treatment being safe and efficient, however the therapeutic experience being limited, it is nec-

essary to be careful and to regularly monitor the fetus using ultrasound and the newborn by performing repeated tests of hemoglobin and bilirubin (15).

Corticosteroids: may represent, in the absence of intravenous immunoglobulin, the first line of treatment. They have relatively fast efficacy and low cost. The response rate to corticosteroids varies between 60-80% (9).

Mechanism of action: Corticosteroids aim at B and T lymphocytes, thus restricting the production of anti-platelet autoantibodies.

Side-effects: the administration of corticosteroids may involve a double risk: maternal and fetal, according to some reports. Corticosteroids are considered a safe method for the fetus; they do not have a teratogenic effect and do not cause toxicity for the fetus since 90% of the administered dose is metabolized in the placenta. Its long-term/ in high dose administration, especially during the first trimester may produce in the fetus: congenital malformations (frequently orofacial malformations), the development of iatrogenic hypercorticism with a possible neonatal corticoadrenal failure. The effect of corticosteroids is lower in the fetus than in the mother, since their concentration in the blood in the umbilical cord is of only 10% of the concentration in the maternal blood.

Dexametasone is more active, as it produces blood concentrations in mother/fetus of 3/1. The side-effects reported in the mother: hyperglycemia, hypokalemia, hypertension, osteoporosis, aggravation of edema, exacerbation of the diabetes preexisting the pregnancy or of gestational diabetes, onset of gestational psychosis or of eclampsia, premature rupture of the membranes (11) and prematurity. The prolonged treatment with cortisone may also associate in the mother: an increased risk of infections, myopathy, cataract, gestational diabetes, psychosis, osteoporosis, bone demineralisation.

Treatment schedule. Treatment may be initiated with 1mg/kg/day prednisone (related to the pregestational weight) with a treatment response in 3 days – 2 weeks, then it is recommended to gradually decrease the dose until the minimum efficient dose is reached in order to maintain a satisfactory/safety level of the platelets (which control the hemorrhagic syndrome). Approximately 80% of the patients initially respond to the cortisone, within a period of 4-6 weeks. After 2-3 weeks of treatment, the dose can gradually be decreased by 10-20% a week, in order to reduce the side-effects (5). In pregnant women where a significant response has not been obtained after 4-6 weeks, the administration of Prednisone should be interrupted because there are few chances of obtaining a late response and the prolonged treatment with cortisone may be associated with adverse effects (as specified above). Dexametasone is recommended especially in the third trimester or before delivery in doses ranging between 8-24 mg iv /day during a period of 4-6 days. During labor, high doses of cortisone may be used: 16 mg iv Dexametasone or 200 mg hydrocortisone hemisuccinate.

In order to avoid adverse reactions, schedules with low doses of cortisone (20 mg/day Prednisone) associated or not with IVIg are used. Some centers use as standard treatment 0.25 mg/kg Prednisolone as the first line of treatment for pregnant women with bleeding risk (12). Most of the pregnant women with ITP have a good response to the treatment, a good tolerance and do not associate adverse reactions. The maintenance treatment with cortisone, in order to maintain a good platelet count for hemostasis, can be used until delivery, without involving the necessity of a complete normalization of the maternal platelet count (7). The studies have shown that the administration of corticosteroids to pregnant women with ITP did not affect the platelet count of the fetus or the appearance of neonatal thrombocytopenia (13,14).

3. Third Line: Splenectomy, combination therapy or other medications

Splenectomy. Usually, splenectomy is rarely indicated, being considered the second or third line of treatment in pregnancy and it can be taken under consideration in selected cases. It induces complete remission in approximately 2/3 of the patients, but it is a delicate procedure during pregnancy due to the fetal risk (abortion, premature delivery), even in the case of a laparoscopic intervention.

Mechanisms. Splenectomy removes the place of platelet destruction, as well as the source of the cells with an immune potential. After a splenectomy, only a reduced number of macrophages capable to destroy the platelets linked to autoantibodies are left. After a splenectomy, the synthesis of autoantibodies by the B lymphocytes is impaired in some patients.

Indications. Splenectomy is indicated for ITP refractory to corticotherapy and intravenous immunoglobulins, in pregnant women during the second trimester, without comorbidities. There are contradictory data regarding the value of anticipating the sensitivity to splenectomy, the most conclusive indicator of sensitivity to splenectomy being the scintigraphy of autologous platelets marked with indium, with an over 90% response if the destruction of the platelets takes place primarily in the spleen. However, studies regarding the sequestration of platelets are performed with difficulty, they are unavailable at present and they are not indicated in pregnant women.

Therapeutic response. Approximately 70-75% of the pregnant patients with ITP may have a significant response to splenectomy (11). In the other patients, the platelet count will register a more reduced increase or will return to normal only temporarily. Most of the relapses occur during the first 6 months post splenectomy; a small number of patients may relapse even after this period.

Adverse effects and complications. If the splenectomy is performed too early (during the first trimester), it may cause an abortion and, during the third trimester, it is associated with a high rate of fetal mortality. The intervention is preferred during the second trimester (when the surgical stress for the mother and the risks for the fetus are minimal) in refractory patients to the other therapeutic lines. Postoperative complications: the pregnant women who have undergone a splenectomy present a low risk of developing generalized post splenectomy sepsis, with a mortality rate estimated at 1.2%.

Procedure. A splenectomy must be preceded, 2 weeks prior to the surgery, by the prophylactic immunization against: Haemophilus influenzae, Streptococcus pneumoniae and Neisseria meningitidis in order to prevent infectious complications and post splenectomy sepsis. The pneumococcal vaccine will be administered repeatedly every 5 years. Antibiotic prophylaxis will be performed (250 mg/day penicillin orally). The optimum period to perform antibiotic prophylaxis has not yet been determined, but the guidelines in Great Britain recommend life-long administration.

Splenectomy in a pregnant woman must take into account the physiological and anatomical changes which occur during the pregnancy. These changes may make laparoscopic splenectomy to be, technically speaking, much more difficult, and that is why the gynecologist and the surgeon have to assess the preoperative clinical state of the pregnant woman, the biological parameters, associated with maternal and fetal ultrasound investigations and inform the pregnant woman on the risks of the surgical intervention (18,19). Some mechanisms were described as leading to an increase of the fetal morbidity and mortality associated with laparoscopic surgery during pregnancy: direct uterine trauma, intra-amniotic CO2 insufflations, trauma to the abdominal organs and vessels, decrease of the blood flow and oxygenation through the uterine vessels, teratogenic effects induced by the anesthetic drugs, fetal acidosis due to the pneumoperitoneum with CO2, the effects of anesthesia on maternal hemodynamics and the acid-base equilibrium, increase of the risk of thromboembolism, the effects of the perioperative and postoperative medication. In the case of pregnant women, particular attention must be paid to the manner in which the cannulas and needles for laparoscopic surgery are placed in order to avoid injuring the uterus and perforating the membranes, which can lead to massive bleeding, infections or gas embolism (18,20).

According to the latest reports, the hemodynamic changes during laparoscopic surgery performed during pregnancy are similar to those occurring in non-pregnant women, the laparoscopic procedure being relatively safe and contributing to the decrease of postoperative complications and to the shortening of the hospital stay. The safest period to perform a laparoscopic splenectomy remains the second trimester of the pregnancy. Most of the data in the literature maintain that laparoscopic splenectomy can be performed safely during the pregnancy if all the necessary safety measures are taken (preoperative care, accuracy of the surgical technique, postoperative care), with a relatively low percentage of possible complications which can vary in point of severity (from minimum local complications up to injuries of the uterus, increase of the intra-abdominal pressure by insufflations, absorption of CO2 by the fetus). The rate and severity of the complications during laparoscopic surgery on a pregnant woman were generally associated with the preexisting pathology/comorbidities of the pregnant woman who underwent surgery (18, 21,22).

The studies have shown that following a splenectomy in the cases with ITP, the platelet count returned to normal, whereas the production of autoantibodies was not influenced, the risk of the appearance of fetal thrombocytopenia persisting due to their crossing through the placenta.

Combination therapy. In non-responders and in some patients' refractory to all lines of treatment, responses may still be obtained by using combination therapy: high-dose corticotherapy (Metilprednisolone 1 g iv) + IGIV 1-2 g/kg.

Other medications. Immunosuppressants, cytostatic drugs or androgens (Cyclophosphamide, Rituximab, Vincristine, Danazol or other androgenic agents) must be avoided during pregnancy, especially during the first trimester, due to teratogenicity, the risk of adverse reactions in the fetus decreasing after the 20th week, but the risk of premature birth persisting (11).

Danazol, still used for the treatment of ITP, could masculinize a female fetus, and that is why it is not recommended during pregnancy.

Immunosuppressants (Imuran, Cyclophosphamide) and cytostatic drugs (Vincristine, Vinblastine) are teratogenic during the first trimester of pregnancy and during the second and third trimesters they may cause delays in intrauterine development and severe fetal dystrophies.

Azathioprine may be used for pregnant women with renal transplantation or inflammatory bowel disease.

Cyclosporin A may be safely used during pregnancy and may be indicated in selected cases.

Rituximab – a monoclonal antibody against the protein CD20, targets CD20+ B lymphocytes which it destroys, leading to the decrease of the production of antiplatelet autoantibodies. It also acts by blocking the FCγ macrophagic receptor. It is indicated for the treatment of chronic ITP which is refractory to the other lines of treatment. It does not have a therapeutic indication in pregnant women with ITP, but it has been used successfully for the treatment of pregnant women with hematological neoplasms (non-Hodgkin lymphomas).

Analogous of thrombopoietin receptor– there are no studies related to pregnant women; they are considered C category drugs for pregnancy (9). Data derived from the use of Eltrombopag in pregnant women are inexistent or limited. Eltrombopag is not recommended during pregnancy and for the women at a fertile age who do not use contraceptive methods. Studies on animals have revealed toxic effects on the reproduction function, but it did not affect fertility in females, the incipient embrionary development or embriofetal development in rats, there was no effect on the embriofetal development in rabbits. The treatment with Eltrombopag was associated with embryonic death, with the decrease of the fetal body weight and of the pregnant uterus in a study on fertility in females, and with a low incidence of the cervical ribs and with a low fetal body weight, in a study regarding embriofetal development (24).

Other methods of treatment

Plasmapheresis – small volumes/appointment can be changed, if repeatedly performed. This method of treatment can be attempted for refractory ITP (5).

Transfusions of platelet mass – are indicated in the cases of potentially lethal hemorrhages, intracerebral hemorrhage or as prophylactic treatment in the cases of severe thrombocytopenia <10000/mmc ,when the pregnant woman is about to undergo any kind of surgery (splenectomy, C-section, various surgical interventions). Steroids in large doses administered intravenously and IVIg can be given together with the platelet transfusion in order to increase the platelet count and to stop the hemorrhage. The life span of the platelets is increased if the platelets are subject to transfusion immediately after the IVIg infusion. ❑

CONCLUSIONS

In ITP during pregnancy, if bleeding symptoms are absent, it is necessary to monitor the platelet count at least every month during the first two trimesters, every two weeks during the third trimester, then every week when the term of delivery approaches (16,17).

The treatment for ITP during pregnancy must be decided according to the platelet count and to the presence of the hemorrhagic syndrome. The patients with a platelet count of >30000/mmc and without hemorrhagic syndrome do not usually require treatment (11). In the presence of moderate/ severe thrombocytopenia, the treatment must be initiated with the purpose of obtaining a platelet count over 50000/mmc in order to obtain adequate hemostasis during delivery and to be able to perform the epidural anesthesia. Anesthesiologists

recommend a platelet count >75000/mmc for epidural anesthesia and >50,000/mmc for a C-section (1,23).

Treatment should be started if the platelet count is <20000-30000/mmc before 36 weeks, in case of symptomatic bleeding during any trimester or if the platelet count <30000-50000/mmc after 36 weeks.

Management before 36 weeks of pregnancy:

a. Asymptomatic patients with moderate thrombocytopenia (platelet count >30000/mmc) – no treatment is necessary, careful monitoring is required;
b. Symptomatic patients or patients with moderate towards severe thrombocytopenia (platelet count <30000/mmc) – treatment with 1mg/kg/day corticosteroids (prednisolone) with a rapid decrease to maintain <30 mg/day (it is safe against fetal secondary effects) AND/OR 1g/kg IVIg – repeated administrations (according to the weight of the patient prior to the period of pregnancy);
c. Severe thrombocytopenia (platelet count <10000/mmc) – high doses of corticosteroids (metilprednisolone/ dexametasone) periodically associated with high doses of IVIg 1g/kg x 2-4 days. In case of non-response, the other treatment methods (second/third line) for refractory ITP can be attempted, including splenectomy, preferably during the second trimester.

Management after 36 weeks of pregnancy:

a. if the platelet count is >50000/mmc - the patients without clotting problems can be allowed to deliver naturally;
b. if the platelet count is <30000-50000/mmc – pulse-therapy with corticosteroids or immunoglobulin administered intravenously are indicated and sustained monitoring. ❑

Conflict of interest: none declared.
Financial support: none declared.

References

1. **Provan D, Stasi R, Newland AC, et al. –** International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia. *BLOOD* 2010; 115(2): 168-186
2. **Thienelt CD, Calverley DC –** Thrombocytopenia Caused by Immunologic Platelet Distruction. Wintrobes Clinical Hematology 2009;II(Chapter 51)
3. **Gill KK, Kelton JG –** Management of Idiopathic Thrombocytopenic Purpura in Pregnancy. *Semin Hematol* 2000; 37:275-289
4. **Jeffrey AL, Murphy LD –** Thrombocytopenia in Pregnancy. *J Am Board Fam Pract* 2002; 15(4):290-297
5. **Vladareanu AM –** Patologia Hematologica a Femeii in Perioada Fertila. Editura Infomedica, decembrie 2007
6. **Schwartz KA –** Gestational Thrombocytopenia and Immune Thrombocytopenia in Pregnancy. *Hematol Oncol Clin North Am* 2000; 14:1101-1106
7. **Cohen DL, Baglin TP –** Assessment and Management of Immune Thrombocytopenia in Pregnancy and in Neonates. *Archives of Disease in Childhood* 1995; 72: F71-F76
8. **Webert KE, Mittal R, Siguoin C, et al. –** A Retrospective 11-Year Analysis of Obstetric Patients with Idiopathic Thromobocytopenic Purpura. *BLOOD* 2003; 102:4306-4311
9. **Keith R. McCrae I** (Cleveland Clinic Foundation) – Thrombocytopenia in Pregnancy. *Hematology* 2010
10. **Douglas BC, Bussel JB –** How I Treat Idiopathic Thrombocytopenic Purpura (ITP). *BLOOD* 2005; 106(7): 2244-2251
11. **Keith R MC –** Trombocytopenia in Pregnancy: differential diagnosis, pathogenesis and management. *Blood* Rewiews 2003; 17:7-14
12. **Bellucci S, Charpak Y, Chastang C, et al. and the Cooperative Group on Immune Thrombocytopenic Purpura –** Low Doses v Conventional Doses of Corticoids in Immune Thrombocytopenic Purpura (ITP). *Blood* 1988; 71:1165-9
13. **Burrows R, Kelton J –** Thrombocytopenia in Pregnancy. Haemostasis and thrombosis in obstetrics and gynaecology by Greer I, Turpie A, Forbes C, eds. London: Chapman & Hall, 1992: 407-29
14. **Karpatkin M, Porges R, Karpatkin S –** Platelet Counts in Infants of Women with Autoimmune Thrombocytopenia, Effect of Steroid Administration to the Mother. *N Engl Jf Med* 1981; 305:936-8
15. **Michel M, Novoa MV, Bussel JB –** Intravenous anti-D as a Treatment for Immune Thrombocytopenic Purpura (ITP) During Pregnancy. *Br J Haematol* 2003; 123:142-146
16. **George JN, Woolf SH, Raskob GE, et al. –** Idiopathic Thrombocytopenic Purpura: a Practice Guideline Developed by Explicit Methods for the American Society of Hematology. *Blood* 1996; 88:3-46
17. **Provan D, Newland A, Bolton-Maggs P, et al. –** Guidelines for the Investigation and Management of Idiopathic Thrombocytopenic Purpura in Adults,Children and in Pregnancy. *Br J Haematol* 2003; 120:574-596
18. **Nollag O, Rourke, Kodali BS –** Laparoscopic Surgery During Pregnancy. *Curr Op in Anaesthesiology* 2006;19(3): 254-259
19. **Stiemer B, Opri F, Senger D, et al. –** Successful Emergency Splenectomy During Pregnancy in a Patient with Life-Threatening Idiopathic Thrombocytopenia. Case report. *J Perinat* ed.1996;24(6):703-6
20. **Jackson H, Granger S, Price R, et al. –** Diagnosis and Laparoscopic Treatment of Surgical Diseases during Pregnancy: an Evidence-Based Review. *Surgical Endoscopy* 2008; 22(9):1917-1927
21. **Griffiths J, Sia W, Shapiro AM, et al. –** Laparoscopic Splenectomy for the Treatment of Refractory Immune Thrombocytopenia in Pregnancy. *J Obstet Gynaecol Can* 2005; 27(8):771-4
22. **Hardwick RH, Slade RR, Smith PA, et al. –** Laparoscopic Splenectomy in Pregnancy. *J Laparoendosc Adv Surg Tech A.* 1999; 9(5):439-40
23. **Douglas MJ –** The Use of Neuraxial Anesthesia in Parturients with Thrombocytopenia: What is an Adequate Platelet count? In: Halpern SH, Douglas MJ, eds. Evidence-Based Obstetric Anesthesia. Malden, MA: Blackwell; 2005
24. **Eltrombopag –** Summary of Product Characteristics.