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REVIEW ARTICLE

Maternal autoimmune disorders and fetal defects

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ABSTRACT

Maternal autoantibodies can cross the placenta and cause fetal damage. This article summarizes the development and management of fetal thyroid goiter in response to maternal Graves' disease and/or its treatment with antithyroid medication, fetal heart block due to maternal anti-Ro and anti-La antibodies, fetal athrogryposis multiplex congenita in association with maternal myasthenia gravis and fetal brain hemorrhage due to maternal autoimmune thrombocytopenia.

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Maternal Graves' disease and fetal thyroid goiter

Maternal Graves' disease

Normally, the hypothalamus produces thyroid-releasing hormone (TRH) which stimulates the pituitary gland to release thyroid-stimulating hormone (TSH) which attaches itself to TSH receptors on the thyroid gland and stimulates the production of thyroid hormones, which in turn control their production through negative feedback on both the hypothalamus and pituitary gland (Figure 1).

Graves' disease, which is found in about one in 500 pregnant women [1], is an autoimmune disorder characterized by the presence of immunoglobulins that bind the TSH receptors in the thyroid gland and stimulate the production of thyroid hormones leading to thyrotoxicosis. Affected individuals are treated by radioiodine therapy to destroy the thyroid gland or surgical removal of the gland followed by the administration of the synthetic thyroid hormone levothyroxine. Some patients are treated by anti-thyroid drugs, such as propylthiouracil and methimazol; these drugs inhibit the enzyme thyroperoxidase which facilitates the addition of iodine to tyrosine in the production of thyroglobulin, an essential step in the formation of thyroid hormones.

Fetal thyroid goiter

Fetal thyroid goiter, observed in about one in 5000 births, is usually due to maternal Graves' disease; development of fetal goiter has been reported in about 10% of mothers with Graves' disease on antithyroid medication [2,3]. Less common causes of fetal thyroid goiter are inadequate or excessive iodine availability or congenital dyshormonogenesis due to defects in genes involved in the pathway of thyroid hormone production.

In Graves' disease, thyroid-stimulating immunoglobulins cross the placenta and when the level is more than three times the upper limit of normal they stimulate the fetal thyroid gland resulting in the development of a hyperthyroid goiter [4]. However, most cases of fetal thyroid goiter are the consequence of fetal hypothyroidism due to transplacentally derived anti-thyroid drugs used for the treatment of maternal hyperthyroidism [2]. In a few cases of Graves' disease, fetal hypothyroidism has been reported in association

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with transplacental passage of maternal thyroid inhibitory immunoglobulins [5].

Thyroid goiter can be diagnosed prenatally by ultrasound with the demonstration of an anterior cervical echogenic mass of variable size (Figure 2). Large fetal goiters may lead to obstruction of fetal swallowing with consequent polyhydramnios and preterm birth, prevention of adequate head flexion during labor resulting in birth dystocia, and compression of the fetal trachea with consequent breathing problems in the neonate, and difficulties in intubation. Additionally, goiters associated with fetal hypothyroidism could result in long-term neurological sequelae.

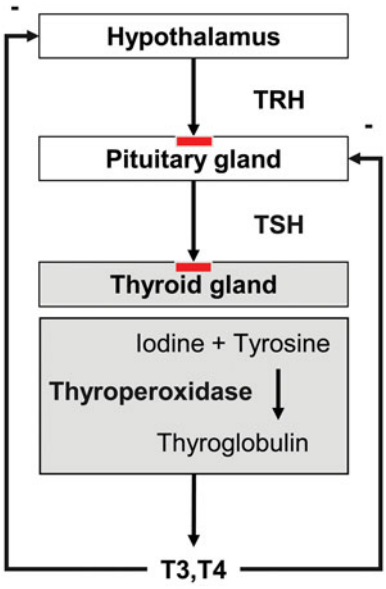

Figure 1. Production of thyroid hormones and its control.

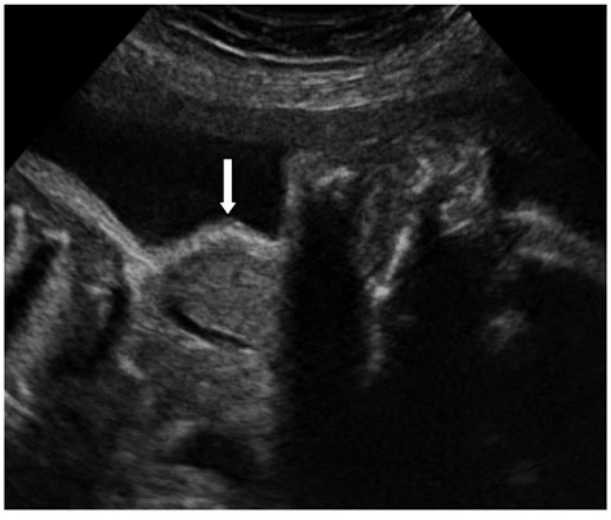

Figure 2. Fetal thyroid goiter (arrow) in a mother with Graves' disease.

Management

In most cases of fetal, thyroid goiter assessment of the maternal condition can help decide whether the cause is fetal hypothyroidism or hyperthyroidism. In uncertain cases, cordocentesis and measurement of fetal blood thyroid hormones and TSH can help distinguish between hypothyroidism, with low thyroid hormones and high TSH, due to antithyroid drugs or congenital dyshormonogenesis, and hyperthyroidism, with high thyroid hormones and low TSH, due to thyroid stimulating immunoglobulins [2,6].

In fetal hyporthyroid goiter, the first-line of treatment is to reduce or even discontinue maternal antithyroid medication aiming to maintain maternal blood thyroxine levels in the upper level of the gestational age-specific normal range (Figure 3) [4]. It should be noted that Graves' disease, like most other autoimmune disorders, improves during pregnancy and consequently requires less medication. The second-line of treatment is intra-amniotic injection of levothyroxine (100 μg/kg) every 1–2 weeks until delivery at term [2]. The goiter usually decreases in size within a few days after the first course of treatment. Subsequent injections are given depending on sonographic evidence of re-enlargement of the gland or serial measurements of levels of thyroid hormones in amniotic fluid or fetal blood [2].

In fetal hyperthyroid goiter, the treatment of choice is administration of antithyroid drugs to the mother (Figure 3). Occasionally, the mother should also be given levothyroxine, as the dose of antithyroid drug can be appropriate for the fetus but could lead to hypothyroidism in the mother. The fetal goiter usually decreases in size within a few days after the initiation of treatment, but if this does not occur measurement

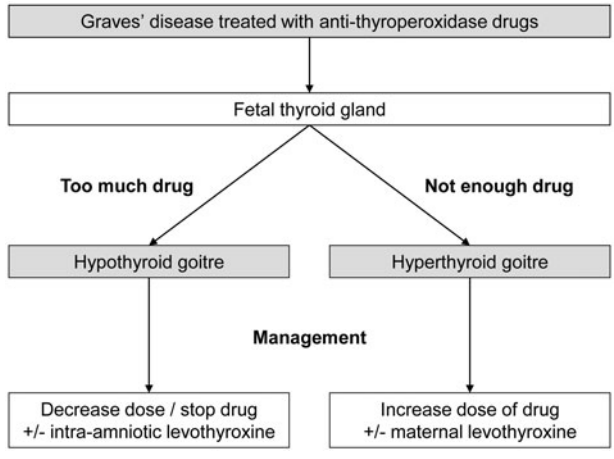

Figure 3. Management of fetal thyroid goiter in maternal Graves' disease.

of levels of thyroid hormones in fetal blood may be needed and the dose of antithyroid drugs given to the mother adjusted as necessary.

Maternal anti-Ro and anti-La antibodies and fetal heart block

Anti-Ro/anti-La antibodies

Anti-Ro and anti-La are a category of autoantibodies directed against nuclear riboproteins. They are frequent not only in autoimmune disease, especially Sjögren syndrome, but also in systemic lupus erythematosus, rheumatoid arthritis or undifferentiated autoimmune disease. However, most of the women carrying these antibodies are asymptomatic with no clinical manifestations of autoimmune disease.

Effect of maternal antibodies on the fetus

Anti-Ro and anti-La antibodies, found in about one in 100 pregnancies, cross the placenta and they can cause fetal heart block, endocardial fibroelastosis, valvular disease, and cardiomyopathy, usually at 16–34 weeks' gestation [7]. The risk of fetal heart block in association with maternal anti-Ro and anti-La antibodies varies between 0.2% and 2% and this is related with the level of anti-Ro antibodies; there may be no risk to the fetus if the maternal antibody level is < 50 U/mL [8].

In about 15% of neonates of mothers with anti-Ro and anti-La antibodies, there is a transient skin rush, liver dysfunction, or pancytopenia; the condition resolves spontaneously within a few weeks after birth.

The risk of anti-Ro- and anti-La antibody-related fetal heart block in pregnancies with a previously affected fetus or neonate is about 15% and this increases to 50% for those with two previously affected pregnancies [7].

Fetal heart block

Fetal heart block is observed in about one in 20,000 live births [7]. Heart block is found in association with cardiac defects, most commonly left atrial isomerism, or in the presence of an otherwise normal heart; the commonest cause of the latter is maternal anti-Ro and anti-La antibodies, but other causes include maternal metabolic disease such diabetes mellitus and phenylketonuria, maternal ingestion of drugs such as lithium, anticonvulsants, or antidepressants and viral infections like coxsackievirus, adenovirus, or cytomegalovirus (Figure 4).

Fetal heart block in the presence of maternal anti-Ro and anti-La antibodies is usually complete and irreversible but can sometimes manifest as a less advanced first- or second-degree block (Figure 5). Third-degree heart block is characterized by total dissociation between atrial and ventricular contractions; none of the atrial contractions reaches the ventricles, which contract at a rate of 50–60 beats per minute. In first-degree block, all atrial contractions and, in the second-degree block, most atrial contractions are conducted to the ventricles but there is prolongation in the interval between atrial and ventricular contractions. The best way to demonstrate fetal heart block is with use of M-mode echocardiography to simultaneously image ventricular and atrial contractions (Figure 6).

Third-degree heart block may lead to impaired left ventricular function, heart failure, and hydrops [7]. About 15% of the affected fetuses or neonates die and 70–80% of survivors require placement of a pacemaker within the first 10 years of life [9–11].

Management

There is no conclusive evidence on the best management of pregnancies with anti-Ro and anti-La antibodies in the presence or absence of fetal heart block.

Causes of fetal heart block
Normal heart: • Anti Ro / La • Diabetes mellitus, phenylketonuria • Anticonvulsants, lithium • Coxsackie virus, cytomegalovirus Abnormal heart: • Heterotaxy syndromes • Transposition of great arteries • Atrial and / or ventricular septal defects • Tetralogy of Fallot

Figure 4. Causes of fetal heart block.

Degrees of fetal heart block	
First:	Prolongation of PR interval between the onset of atrial (P) and ventricular (R) contraction
Second:	Most atrial contractions transmitted to the ventricles
Third:	No atrial contractions transmitted to the ventricles

Figure 5. Degrees of fetal heart block.

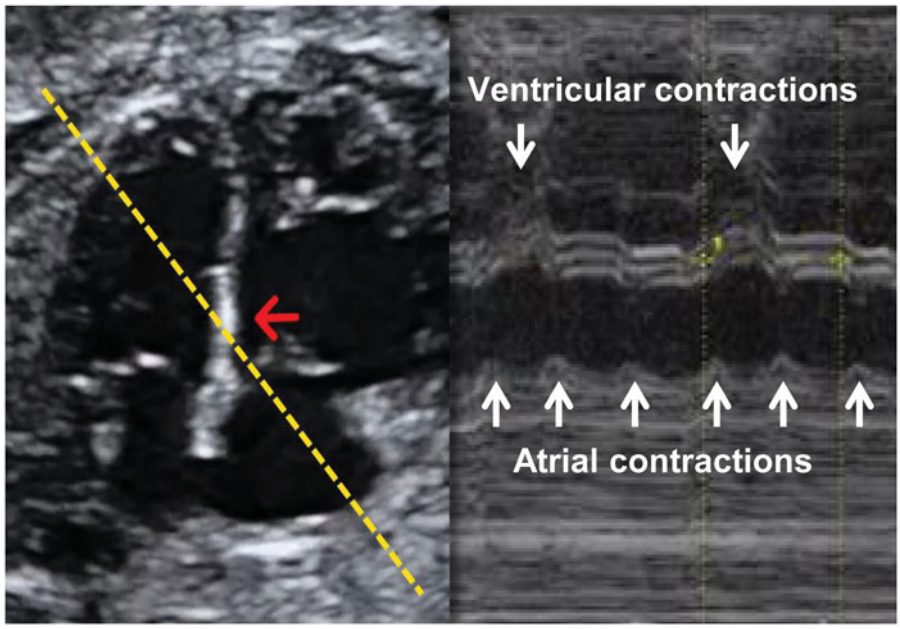

Figure 6. M-mode fetal echocardiography demonstrating third degree heart block.

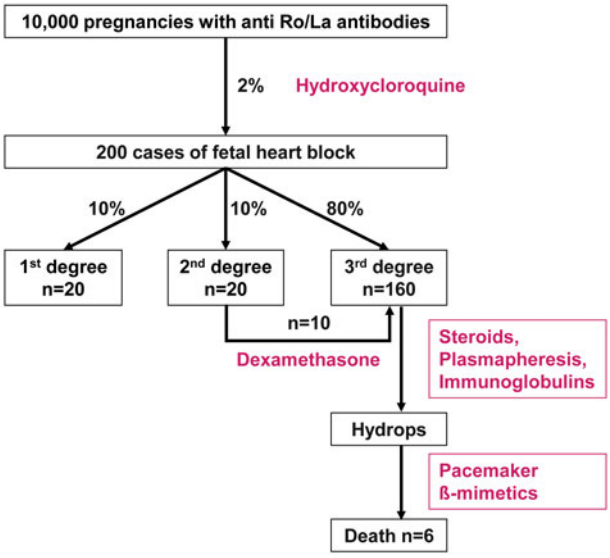

Figure 7. Management of pregnancies with anti-Ro and anti-La antibodies.

However, large retrospective studies have addressed this issue and provide some evidence (Figure 7).

Prevention of fetal heart block in pregnancies with anti-Ro and anti-La antibodies

The antimalarial drug hydroxycloroquine is highly effective in the treatment of skin rashes, pains, and fatique associated with SLE. The drug is safe in pregnancy and there is some evidence that in SLE patients with anti-Ro and anti-La antibodies use of the drug can reduce the risk of development of fetal heart block [12].

One approach in the management of pregnancies with maternal anti-Ro and anti-La antibodies is to perform fetal echocardiography at 1–2 weekly intervals from 16 to 34 weeks' gestation to monitor the interval between atrial and ventricular contractions. Pregnancies with prolonged interval could be treated with maternal administration of dexamethasone or betamethasone which cross the placenta and can potentially prevent progression to third degree heart block [9,13]. The arguments against such strategy are first, most cases presenting with third degree heart block had normal cardiac function 1–2 weeks previously and secondly, first degree block is usually transient or sustained rather than progressive [7]. The argument in favor of monitoring is that even if the number of cases with second-degree block that can be prevented from developing third-degree block is very small it may be worth the effort of close monitoring of large numbers of pregnancies for the benefit of few; however, 10,000 pregnancies with maternal anti-Ro and anti-La antibodies would require weekly monitoring from 16 to 34 weeks to identify about 20 with second-degree block and if these 20 cases are treated by dexamethasone, only five rather than 10 would progress to third-degree block.

In pregnancies with a previously affected fetus or neonate, where the risk of recurrence is about 15%, there is some evidence that the prophylactic use of hydroxycloroquine could reduce the risk of such recurrence [14], but conclusive evidence is awaited from an ongoing randomized controlled trial. Studies investigating the potential value of prophylactic use of

immunoglobulins in the prevention of third-degree heart block have reported that such therapy is not useful.

Prevention of progression of fetal heart block to heart failure and hydrops

In third-degree heart block, there is fibrosis and calcification of the atrio-ventricular node and this condition is irreversible. The objective in the management of affected fetuses is prevention of fetal hydrops and intrauterine death. Maternal administration of steroids in pregnancies with non-hydropic fetuses with third-degree heart block has not been found to be beneficial in preventing the development of heart failure, hydrops, or death [9,13].

Prevention of progression of fetal heart block with hydrops to death

In hydropic fetuses with third-degree heart block, the prognosis is very poor. Attempts at intrauterine placement of pacemakers have been unsuccessful [15]. There is unproven evidence concerning the possible benefit of maternal administration of Dexamethasone. If the ventricular rate is $<$60 bpm the maternal administration of ß-2 agonists, such as salbutamol or terbutaline, could result in a temporary small increase in the ventricular rate and improve cardiac function [16].

Maternal myasthenia gravis and fetal athrogryposis multiplex congenita

Maternal myasthenia gravis

Normally, motor neurons release acetylcholine which binds to receptors in muscles and stimulates their contraction (Figure 8). Acetylcholine is then degraded by the enzyme acetylcholinesterase.

In myasthenia gravis, which is found in about one in 30,000 pregnant women [17], autoantibodies are directed against the acetylcholine receptors at the neuromuscular junction of the skeletal muscles. The clinical feature of the condition is fluctuating painless muscle weakness with remissions and exacerbations involving one or several skeletal muscle groups.

Medical treatment of myasthenia gravis is aimed at first, increased availability of acetylcholine at the neuromuscular junction by drugs, such as pyridostigmine, which inhibit the enzyme acetylcholinesterase; second, suppression of the production of autoantibodies by prednisolone; third, reduction in the maternal concentration of autoantibodies by plasmapheresis; and fourth, blockage of the effect of autoantibodies by intravenously administered immunoglobulines. Surgical treatment involves excision of the thymus gland which in myasthenia gravis is enlarged and abnormal.

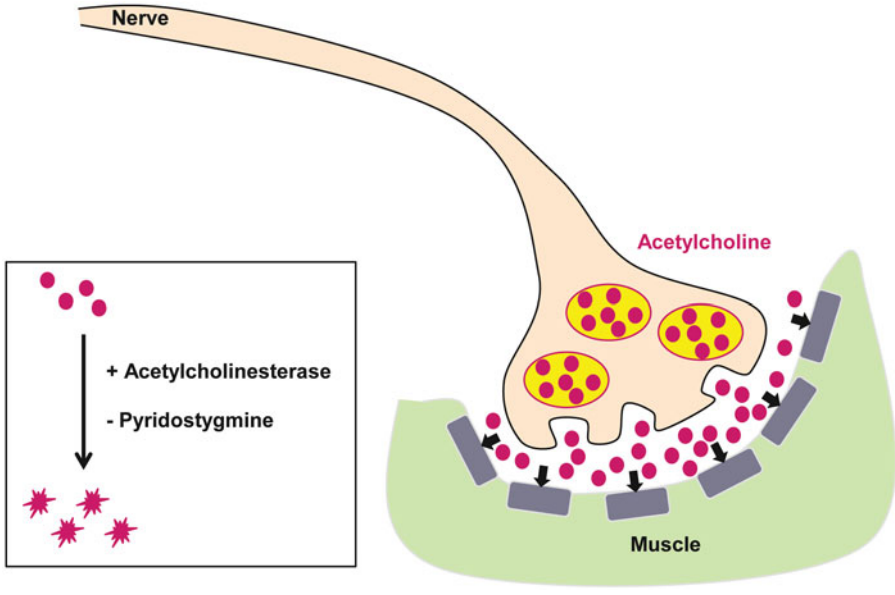

Figure 8. Acetylcholine (circles) held in vesicles at the nerve ending is released into the neuromuscular junction in response to a nerve impulse, binds to receptors in muscles (box) and stimulates their contraction. Acetylcholine is then degraded by the enzyme acetylcholinesterase, which is inhibited by the drug pyridostigmine.

Effect of maternal antibodies on the fetus

During pregnancy, anti-acetylcholine receptor antibodies can cross the placenta and in about 2% of cases they cause arthrogryposis multiplex congenita [18]. The antibodies also cause transient neonatal myasthenia gravis in about 15% of cases [19]; affected neonates have feeding and respiratory difficulties that develop usually within 12 h to several days after birth but resolve over a period of 3 weeks as the maternal antibodies are cleared from the neonatal circulation.

Fetal arthrogryposis congenita is thought to result from placental passage of maternal antibodies directed against the fetal-type of acetylcholine receptor (Figure 9) [20]. These receptors are found in fetal muscles in the early stages of pregnancy and are completely replaced by the adult-type by 33 weeks' gestation. Mothers carrying the fetal-type of receptor antibodies are often asymptomatic because these antibodies do not act on the adult-type of receptor normally found in maternal muscles; however, later in life these women may develop the disease as they go on to also produce antibodies against the adult-type of receptors. It could, therefore, be suggested that impaired fetal movements during the second trimester, as a consequence of antibodies directed against the fetal-type acetylcholine receptor, would lead to arthrogryposis multiplex congenital, whereas predominance of antibodies directed against the adult-type of the receptor would cause transient neonatal myasthenia gravis.

The risk of arthrogryposis multiplex congenita due to maternal myasthenia gravis in pregnancies with a previously affected fetus is up to 100% [21].

Fetal arthrogryposis multiplex congenita

Arthrogryposis multiplex congenita, observed in about one in 3000 births, results from lack of fetal movements and it is characterized by non-progressive contractions in more than two joints in multiple body areas [22]. Maternal myasthenia gravis accounts for <1% of cases of arthrogryposis multiplex congenita; the vast majority of cases are due to genetic and chromosomal abnormalities, brain and spinal defects, oligohydramnios, and viral infections [23].

Prenatal diagnosis by ultrasound relies on the demonstration of lack of movement and abnormal position with fixed flexion or extension deformities in fetal joints (Figure 10). In severe cases, multiple joints are affected and polyhydramnios develops due to impaired fetal swallowing.

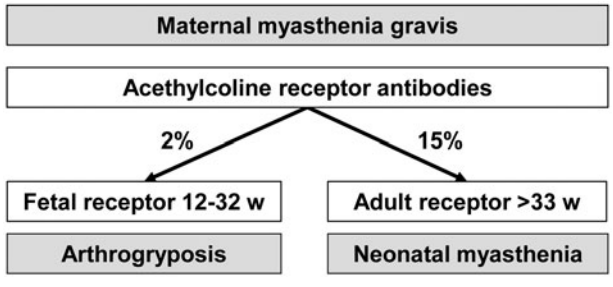

Figure 9. Consequences of maternal myasthenia gravis on the fetus.

Management

In cases with established arthrogryposis multiplex congenita maternal treatment with plasmapheresis, intravenous immunoglobulin or pyridostigmine was not found to improve neonatal outcome [21].

In women with myasthenia gravis and history of previously affected pregnancy, the risk of recurrence of fetal arthrogryposis may be decreased by thymectomy before another pregnancy. The effectiveness of alternative strategies during pregnancy, including plasmapheresis, intravenous immunoglobulin, azathioprine, and high doses of pyridostigmine and prednisolone started early in the first trimester, is controversial [20,21].

Maternal autoimmune thrombocytopenia and fetal brain hemorrhage

Maternal immune thrombocytopenia

Autoimmune thrombocytopenia, found in about one in 500 pregnancies [24], is caused by antibodies directed against platelet membrane glycoproteins (Figure 11). The features are low platelet count and mucocutaneous bleeding. About one-third of the affected women require treatment during pregnancy, usually in the third trimester, with either

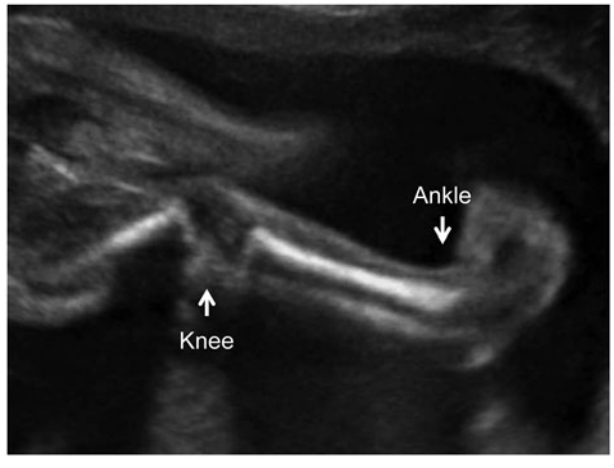

Figure 10. Fetal arthrogryposis with flexion deformity of the knee and talipes.

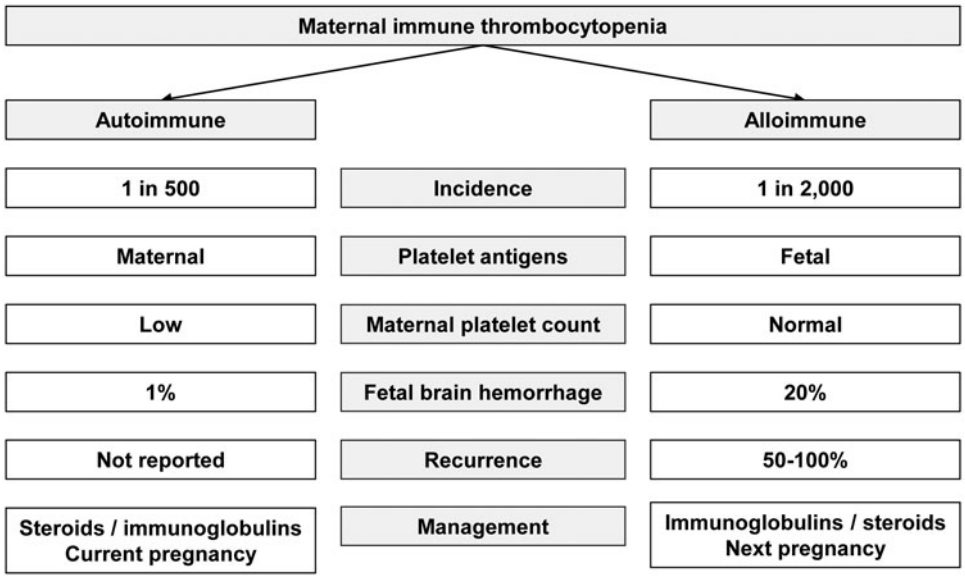

Figure 11. Maternal autoimmune and alloimmune thrombocytopenia.

corticosteroids or intravenous immunoglobulin to increase the platelet count to >50,000/μL; this threshold is considered safe for epidural anesthesia and delivery be cesarean section [25].

In maternal alloimmune thrombocytopenia, found in about one in 2000 pregnancies, there is maternal sensitization to paternally derived antigens on fetal platelets [26]; maternal platelets are not affected.

Effect of maternal antibodies on the fetus

During pregnancy, maternal antiplatelet antibodies can cross the placenta and cause fetal thrombocytopenia; in about 1% of the cases, the thrombocytopenia is severe with consequent fetal intracranial hemorrhage [24,27]. In alloimmune thrombocytopenia, the risk of fetal intracranial hemorrhage is 20% [26]. Autoimmune and alloimmune thrombocytopenia are also associated with transient neonatal thrombocytopenia characterized by development of petechie, echymoses, or melena.

Recurrence of fetal intracranial hemorrhage in mothers with autoimmune thrombocytopenia has not been reported; however, neonatal thrombocytopenia is known to occur more frequently in neonates with a sibling affected by the same condition [27]. In alloimmune thrombocytopenia, the risk of recurrence of fetal intracranial hemorrhage is up to 100% if the father is homozygous for the relevant platelet antigen and 50% if he is heterozygous.

Fetal intracranial hemorrhage

Intracranial hemorrhage is observed in about one in 1000 neonates and, in most cases, this is due to prematurity. Other causes are trauma, alloimmune thrombocytopenia, and maternal ingestion of warfarin. Maternal autoimmune thrombocytopenia accounts for a small proportion of cases.

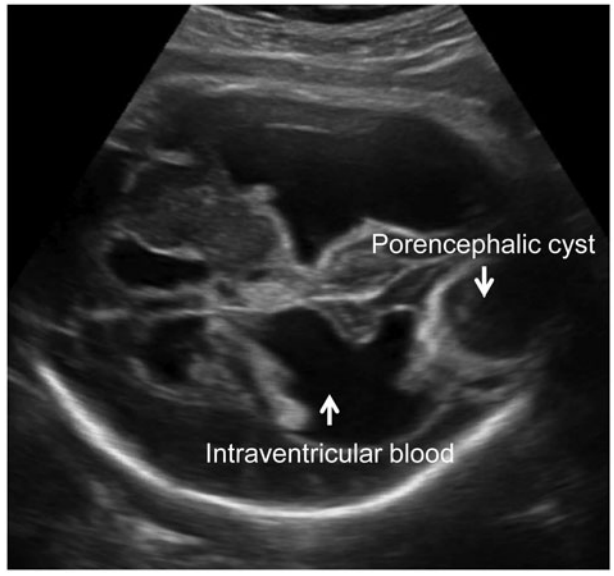

Figure 12. Fetal ventriculomegaly with porencephalic cyst due to intracranial hemorrhage.

Prenatal diagnosis by ultrasound relies on the demonstration of clots within the lateral cerebral ventricles and, in some cases, there is ventriculomegaly due to obstruction of the aqueduct of Sylvius [28]. In severe cases, there is intracerebral hemorrhage and development of porencephaly (Figure 12). Occasionally the fetus may become severely anemic and may develop hydrops. The condition is associated with increased risk of perinatal death and neurodevelopmental delay,

particularly in cases with cerebral parenchymal involvement.

Management

The management of pregnancies with autoimmune thrombocytopenia is essentially based on serial measurements of maternal platelet counts and treatment with corticosteroids or intravenous immunoglobulin if the count drops to below 50,000/μL [29].

In pregnancies with alloimmune thrombocytopenia, intravenous immunoglobulin infusions are given on a weekly basis; the gestational age at onset of such therapy is about 10 weeks before the gestational age of an adverse event in a previously affected pregnancy, including fetal brain hemorrhage, neonatal thrombocytopenic purpura, or bruising [30].

Disclosure statement

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References

[1] Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol. 2013;1:238–249.
[2] Bliddal S, Rasmussen AK, Sundberg K, et al. Antithyroid drug-induced fetal goitrous hypothyroidism. Nat Rev Endocrinol. 2011;7:396–406.
[3] Rosenfeld H, Ornoy A, Shechtman S, et al. Pregnancy outcome, thyroid dysfunction and fetal goitre after in utero exposure to propylthiouracil: a controlled cohort study. Br J Clin Pharmacol. 2009;68:609–617.
[4] Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21:1081–1125.
[5] Brown RS, Bellisario RL, Botero D. Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. J Clin Endocrinol Metab. 1996;81:1147–1151.
[6] Kilpatrick S. Umbilical blood sampling in women with thyroid disease in pregnancy: is it necessary? Am J Obstet Gynecol. 2003;189:1–2.
[7] Brito-Zerón P, Izmirly PM, Ramos-Casals M, et al. The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol. 2015;11:301–312.
[8] Jaeggi E, Laskin C, Hamilton R, et al. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. J Am Coll Cardiol. 2010;55:2778–2784.
[9] Eliasson H, Sonesson SE, Sharland G, Fetal Working Group of the European Association of Pediatric Cardiology, et al. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation. 2011;124:1919–1926.
[10] Levesque K, Morel N, Maltret A, et al. Description of 214 cases of autoimmune congenital heart block: results of the French neonatal lupus syndrome. Autoimmun Rev. 2015;14:1154–1160.
[11] Izmirly PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation. 2011;124:1927–1935.
[12] Izmirly PM, Kim MY, Llanos C, et al. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. Ann Rheum Dis. 2010;69:1827–1830.
[13] Izmirly PM, Saxena A, Sahl SK, et al. Assessment of fluorinated steroids to avert progression and mortality in anti-SSA/Ro-associated cardiac injury limited to the fetal conduction system. Ann Rheum Dis. 2016;75:1161–1165.
[14] Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation. 2012;126:76–82.
[15] Eghtesady P, Michelfelder EC, Knilans TK, et al. Fetal surgical management of congenital heart block in a hydropic fetus: lessons learned from a clinical experience. J Thorac Cardiovasc Surg. 2011;141:835–837.
[16] Robinson BV, Ettedgui JA, Sherman FS. Use of terbutaline in the treatment of complete heart block in the fetus. Cardiol Young. 2001;11:683–686.
[17] McGrogan A, Sneddon S, de Vries CS. The incidence of myasthenia gravis: a systematic literature review. Neuroepidemiology. 2010;34:171–183.
[18] Hoff JM, Daltveit AK, Gilhus NE. Artrogryposis multiplex congenita – a rare fetal condition caused by maternal myasthenia gravis. Acta Neurol Scand Suppl. 2006;183:26–27.
[19] Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis: consequences for pregnancy, delivery, and the newborn. Neurology. 2003;61:1362–1366.
[20] Vincent A, McConville J, Farrugia ME, et al. Antibodies in myasthenia gravis and related disorders. Ann N Y Acad Sci. 2003;998:324–335.
[21] Polizzi A, Huson SM, Vincent A. Teratogen update: maternal myasthenia gravis as a cause of congenital arthrogryposis. Teratology. 2000;62:332–341.
[22] Hall JG. Arthrogryposis multiplex congenita: etiology, genetics, classification, diagnostic approach, and general aspects. J Pediatr Orthop B. 1997;6:159–166.
[23] Rink BD. Arthrogryposis: a review and approach to prenatal diagnosis. Obstet Gynecol Surv. 2011;66:369–377.

[24] Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. N Engl J Med. 1993;329:1463–1466.
[25] Martí-Carvajal AJ, Peña-Martí GE, Comunián-Carrasco G. Medical treatments for idiopathic thrombocytopenic purpura during pregnancy. Cochrane Database Syst Rev. 2009;4:CD007722.
[26] Bussel JB, Zacharoulis S, Kramer K, et al. Clinical and diagnostic comparison of neonatal alloimmune thrombocytopenia to non-immune cases of thrombocytopenia. Pediatr Blood Cancer. 2005;45:176–183.
[27] Webert KE, Mittal R, Sigouin C, et al. A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. Blood. 2003;102: 4306–4311.
[28] Ghi T, Simonazzi G, Perolo A, et al. Outcome of antenatally diagnosed intracranial hemorrhage: case series and review of the literature. Ultrasound Obstet Gynecol. 2003;22:121–130.
[29] Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. Blood. 2013;121:38–47.
[30] Bussel JB, Berkowitz RL, Lynch L, et al. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low-dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol. 1996;174:1414–1423.