14, 2000, č. 1, s. 11–14

PREHĽADNÝ REFERÁT *REVIEW*

SYSTÉMOVÁ SKLERÓZA A GRAVIDITA

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SYSTEMIC SCLEROSIS AND PREGNANCY

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Summary
Objective: **Review studies on systemic sclerosis and pregnancy.**
Methods: **Analysis of case reports and prospective and retrospective studies.**
Main results: **Early case reports reported a 50 % pregnancy loss rate, but later retrospective and prospective case-control studies have found pregnancy loss varying between 9–45 %. Recent studies found cutaneous disease largely unaltered by pregnancy whereas arthralgias and gastroesophageal reflux sometimes increased. Development of renal crisis was not found increased in pregnant patients, but could be controlled with ACE-inhibitors when occurring. Tight skin of widespread cutaneous disease can create difficulties at delivery. Systemic sclerosis does not cause neonatal disease, but the limited form increases the risk of perinatal mortality.**
Conclusion: **Pregnancy is possible in patients with systemic sclerosis, but should be discouraged in those with early, diffuse sclerosis or pulmonary hypertension. Pregnant patients should be monitored regularly during pregnancy.**
Key words: systemic sclerosis, pregnancy, pregnancy loss rate, perinatal mortality.

Súhrn
Cieľ: **Analyzovať štúdie o systémovej skleróze a tehotnosti.**
Metódy: **Analýzy prípadových štúdií a prospektívnych aj retrospektívnych štúdií.**
Hlavné výsledky: **Staršie prípadové štúdie udávajú 50 % potratovosť, no v neskorších prospektívnych aj retrospektívnych štúdiách typu „case-control" potratovosť kolíše medzi 9 % až 45 %. Nedávne štúdie zistili, že tehotnosť väčšinou neovplyvní kožné ochorenie, no niekedy sa pri ňom zintenzívni artralgia a gastroezofágový reflux. U tehotných pacientok sa indukovanie renálnej krízy tehotnosťou nepozorovalo. Keď sa objaví, dá sa udržať pod kontrolou inhibítormi ACE. Pri pôrode môže robiť problémy napätá koža, ktorá sa vyskytuje pri veľmi rozšírenej kožnej chorobe. Systémová skleróza neprechádza na novorodenca, no v obmedzených prípadoch zvyšuje pravdepodobnosť perinatálneho úmrtia.**
Záver: **Ženy so systémovou sklerózou môžu otehotnieť, no tehotnosť sa neodporúča pacientkám s ranou, difúznou sklerózou, či pľúcnou hypertenziou. Tehotná pacientka musí počas tehotnosti chodiť na pravidelné kontroly.**
Kľúčové slová: systémová skleróza, gravidita, potratovosť, perinatálna úmrtnosť.

Systemic sclerosis is a rare connective tissue disease with both inflammatory and vascular changes in the skin and internal organs. Typical clinical manifestations are Raynaud's phenomenon, tight skin and manifestations from the lung, heart, kidney and gastrointestinal tract. The disease can manifest as a limited or systemic condition, and varies regarding the extent of skin and organ involvement and progress of the disease. Diffuse visceral scleroderma and particularly renal and lung involvement carry a serious prognosis. At present there is no satisfactory therapy for the disease.

Systemic sclerosis has a female prepomderance of about 8–10:1 in reproductive years (1). Onset of symptoms occurs predominantly in the early 40's. As modern women often choose to postpone pregnancy, patients with systemic sclerosis have the potential to become pregnant.

In the 1960ies and 70ies published reports on the concurrence of pregnancy and systemic sclerosis were rare and consisted mostly of case reports with often unfavourable maternal and fetal outcome. This resulted in the view held by many doctors that patients with systemic sclerosis should not become pregnant. However, several retrospective case-control studies and one prospective study have changed this concept. This chapter summarizes aspects of reproduction in women with systemic sclerosis.

MICROCHIMERISM AND SCLERODERMA

Systemic sclerosis has a marked similarity to chronic graft-versus-host disease, and this has prompted research into the

role of microchimerism in the pathogenesis of scleroderma. Englert and Silman have hypothesized that blighted pregnancies could result in transplacentar transfer of fetal cells leading to a chronic graft-versus-host disease (2). A recent study has shown excess maternal-fetal HLA class II compatibility in women with systemic sclerosis compared to healthy controls (3). Chronic graft-versus-host disease due to persistent fetal cells in the mothers circulation may be a pathogenetic factor. However not all studies have found that a pregnancy or an adverse reproductive history preceeds the onset of systemic sclerosis.

FERTILITY

It was initially suggested that fertility may be decreased in women with systemic sclerosis and some authors found indeed few pregnancies in their female patients (4, 5). However, these observations could easily be explained by confounding factors like age, a decision against pregnancy after disease onset or reduced libido. Two British studies have found reduced fertility with a delay in conception in women with systemic sclerosis compared to healthy controls (2, 4). Other case-control studies have not been able to find diminished fertility (7, 8). However the timing of pregnancy and the onset of disease was not always stated. Some reports indicate that fertility indeed may be impaired in women with localised scleroderma in genital areas, particularly if this interferes with sexual intercourse (9, 11).

PREGNANCY OUTCOME

Pregnancy outcome has varied in the literature (12, 13). The early case reports reported a 50 % pregnancy loss rate, but later series of retrospective and case control studies have found much more favourable pregnancy outcomes (13). Several retrospective case-control studies have found an increased ferquency of miscarriages (17–45 %) in women with systemic sclerosis compared to healthy controls or to women with rheumatoid arthritis (RA) (2, 5, 6, 7, 10). Miscarriages were mostly first trimester losses. They were independent of the type of systemic sclerosis and the extent of organ involvement. Interestingly, an increased rate miscarriages was found even before disease onset by some studies (2, 10). Since systemic sclerosis often has an insidious onset, subclinical disease may affect placentar blood flow even in women who have not yet developed the full-blown symptoms of the disease. However not all studies have found increased fetal loss. In the American case-control study in women with at least one pregnancy during systemic sclerosis, no increase of miscarriage was found compared with women with RA and normal controls (8). Over all the miscarriage rate in patients with systemic sclerosis was low (9 %).

THE EFFECT OF PREGNANCY ON SYSTEMIC SCLEROSIS

Early case reports described deterioration of systemic sclerosis in more than 50 % with a high proportion of maternal death due to renal failure, pulmonary hypertension and other complications (14). Obviously these case reports were biased towards patients with severe systemic disease and negative outcomes. Retrospective, uncontrolled series including more patients with the limited form of systemic sclerosis showed a much better prognosis (13). Recently 2 retrospective and 1 prospective study described successful pregnancies for the majority of patients (8, 10). In a review of the 27 case reports no change of disease was found in 33 %, deterioration in 44 % and improvement in 11 % during pregnancy (14). In the uncontrolled retrospective series the disease was unchanged in 34 %, deteriorated in 30 % and improved in 11 % (14). A retrospective study of 61 pregnancies noticed no change in 30 %, improvement in 33 % and worsening in 18 % (10). In the retrospective controlled study of 86 pregnancies performed by Steen no change of symptoms during pregnancy was found in 88 %, improvement in 5 % and worsening in 7 % (8). Similar findings were made in the prospective study of 67 pregnancies in 50 women with systemic sclerosis (15).

Only few of the studies have given any detailed description of the influence of pregnancy on particular organ manifestations of systemic sclerosis. One reason may be that symptoms of pregnancy often are similar to manifestations of systemic sclerosis. This is true for backpain, arthralgias, carpal tunnel syndrome, gastroesophageal reflux and dyspnoe. Surveying available data shows that cutaneous disease is not much changed during pregnancy (4, 8, 10). Abdominal wall thickening has not been described as a serious problem in late pregnancy or during parturition in patients with systemic sclerosis. This may be due to the hormone relaxin which greatly increases during pregnancy and induces skin elasticity and loosening of pelvic ligaments. Relaxin is under investigation as a treatment for scleroderma (16). Arthralgias can increase during pregnancy, and gastrointestinal reflux as a rule worsens during the last trimester. Raynaud's phenomenon is mostly improved during pregnancy (8). Mild cardiovascular disease seems not to deteriorate significantly. However pulmonary hypertension carries a severe prognosis during pregnancy and is associated with maternal mortality (17).

Systemic sclerosis can start during a pregnancy and has been described to worsen after pregnancy in a proportion of women (13). However no study has prospectively investigated the postpartum course of systemic sclerosis and thus it is impossible to know if the disease is prone to a postpartum flare or worsens the long-term prognosis of systemic sclerosis.

RENAL DISEASE

Renal disease and the risk of developing renal crisis is one of the most serious complications of systemic sclerosis. In the early case reports, renal failure was the most common cause of maternal death (13, 14). Renal involvement may present as sudden onset malignant hypertension or as rapidly progressing renal failure. Risk factors for renal crisis are: early diffuse systemic sclerosis and rapidly progressing skin disease. Treatment with high dose prednisolon may be an additional risk factor (18). In the early case reports 33 % of mothers developed renal crisis, most of them postpartum (14). In the retrospective, case-control study of Steen, renal crisis occurred in 2 % of pregnancies, and in her prospective study 11 % of patients with diffus scleroderma developed renal crisis during the second trimester (8, 15). However, the frequency of renal crisis was not increased during pregnancy compared to nonpregnant patients with systemic sclerosis (8). The complication occurred only in patients with early diffuse scleroderma. One of the mothers died, the other patients were successfully treated with ACE inhibitors (13). Successful pregnancy after the occurrence of renal crisis have been described (13, 19). In the majority of cases, renal crisis developed in normotensive patients without a previous history of renal disease. Renal involvement can appear at any stage of pregnancy and necessitates differential diagnosis with toxemia of pregnancy. However, the frequency of preeclampsia is not increased in systemic sclerosis.

DELIVERY

Widespread diffuse systemic sclerosis may cause problems related to delivery. Tight, thickened skin can impair access for venupuncture. A reduced oral aperture may render intubation difficult (20). Taught skin of the abdomen and the vagina colud interfere with progress of parturiton. One study reported difficulties during delivery due to a tight vagina and/or perineum in a large proportion of patients with systemic sclerosis. A large episiotomy was required in these patients (10). Contractures of the hips or other large joints can make positioning for delivery difficult. It is not known how often problems like this occur, but they should be considered and probably discussed with the anesthesiologist and obstetrician. There are no reports which have documented a delay in wound healing after Cesarean section or episiotomy in patient with systemic sclerosis.

THE NEONATE

Some autoantibodies present in patients with connective tissue diseases can cause disease in the neonate due to placentar passage. Neonatal lupus syndromes due to anti-SSA/SSB and rare cases of neonatal antiphospholipid antibody syndrome in infants with antiphospholipid antibodies are examples. Systemic sclerosis does not cause neonatal disease nor is the condition hereditary. Perinatal health has only infrequently been addressed, but a case-control study showed no significant increase in prinatal death compared to controls (8). Interestingly, all perinatal deaths occurred in mothers with limited cutaneous disease.

DRUG THERAPY DURING PREGNANCY IN SYSTEMIC SCLEROSIS

Systemic sclerosis is treated with a variety of drugs. Medication during pregnancy will depend on the type of organ manifestation. Arthralgia or synovitis may require treatment with non-steroidal antiinflammatory drugs (NSAIDs). The recommendations for use of NSAID during pregnancy are given in another chapter.

Raynaud's phenomenon is treated with calcium channel blockers, most often in the form of nifedipine. In patients who do not improve of Raynaud's symptoms, nifedipine may be continued during pregnancy. A case report described a successful pregnancy in a patient with serious Raynaud's phenomenon treated with nifedipine (21). Nifedipine crosses the placenta, but no teratogenic of fetotoxic effect have been documented (22). The drug does not adversely affect birth weight.

Occurrence of renal crisis during pregnancy may necessitate immediate antihypertensive treatment. The most effective are the ACE inhibitors, but they must be used with great caution and only if strictly necessary. The ACE inhibitor captopril, enalapril and lisinopril do cross the placenta in significant amounts (23). Renal excretion of the active drug in the fetus has been presummed, rendering swallowing and recirculation of the drug possible.

ACE inhibitors are not teratogenic during the first trimester, but can cause fetal and neonatal injury when administered later in pregnancy. Calvarial hypoplasia, pulmonal anuria and death have been reported (23). It is believed that marked and prolonged fetal hypotension as well as inhibition of growth factors are contributing to the serious fetal and neonatal effects observed after intrauterine exposure to ACE inhibitors.

Corticosteroids are rarely indicated in systemic sclerosis, but may be of use in those with accompanying myositis. Continuation of corticosteroids, at least in high doses, is not recommended in pregnant patients with diffuse systemic sclerosis because of increasing the risk of renal crisis. A case-control study found use of corticosteroids a precipitating factor for development of renal crisis (18).

The use of penicillamine during pregnancy is controversial since there is an about 5 % risk of the develop-

ment of a collagen defect if the fetus is expossed to penicillamine antenatally. The drug should be truly avoided during pregnancy (24). Cytotoxic drugs like methotrexate and cyclophosphamide have been used in severe complications of systemic like pulmonary involvement and myositis. Because of their teratogenic potential, cytostatic drugs are strictly contraindicated during pregnancy and must be withdrawn at least 3 months prior to a planned pregnancy.

Pregnancy and systemic sclerosis should be planned and a detailed clinical and laboratory examination done before conception is warranted. Patients with early diffuse systemic sclerosis, serious pulmonary disease, myocardial involvement or renal scleroderma should be discouraged to become pregnant. The pregnant patient with systemic sclerosis should be monitored by specialists experienced in the disease. Frequent monitoring of renal function and fetal growth is necessary. Controls in the 1st and 2nd trimester should be each fortnight, thereafter each week. There should be a regular follow-up after delivery.

CONCLUSION

A successful pregnancy is possible in patients with systemic sclerosis. However patients with multiple organ manifestations and widespread cutaneous involvement must be regarded as high risk and need care by a team of specialists. Close follow-up of pregnant patients with systemic sclerosis is indicated at all stages of pregnancy and postpartum.

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Do redakcie došlo 3.2.1999.

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