

From THE DEPARTMENT OF MEDICINE
Karolinska Institutet, Stockholm, Sweden

PREGNANCY IN RO/SSA POSITIVE WOMEN

Joanna Tingström



**Karolinska
Institutet**

Stockholm 2013

All previously published papers were reproduced with permission from the publisher.

Cover picture © Claes Gustavsson

Published by Karolinska Institutet. Printed by Larserics Digital Print AB

© Joanna Tingström, 2013
ISBN 978-91-7549-102-8

To my family!

ABSTRACT

Congenital heart block (CHB) may develop in the fetus during pregnancy in Ro/SSA positive women. It is a rare but life-threatening disease and the most serious manifestation of neonatal lupus erythematosus (NLE). The frequency of CHB in Ro/SSA autoantibody positive pregnancy is 1-2%, with a recurrence rate of 12-17%. Development of CHB may be monitored by Doppler/echocardiography examinations during gestational week (GW) 18-24 when early signs of CHB are most likely to occur. The surveillance enables early treatment and may reverse the inflammatory process in the fetal heart. Although this has been known for a decade, little is known about how Ro/SSA autoantibody positive mothers experience their pregnancy when being at risk for having a child with CHB or actually give birth to a child with CHB. Furthermore little is known about the neurodevelopment in the children born with CHB. The aim of this thesis was therefore to investigate Ro/SSA autoantibody positive women's experience of pregnancy and the postnatal period as well as neurodevelopment in children with CHB.

A main finding of the studies is that the awareness and knowledge of Ro/SSA autoantibodies and associated risk for CHB is low both among health care personnel as well as women/families involved. Further, there is a lack of adequate and sufficient information available. The majority of the participants in the study received the information of their own autoantibody positivity as well as the connection to risk for CHB when they were already pregnant. Most women stated that they wanted the information as soon as the autoantibody positivity was known, if possible before pregnancy in order to prepare and adjust to the situation. The majority of the women also stated that the information would not have influence their decision of becoming pregnant. A majority of the women giving birth to children with CHB stated that they did not receive enough information. Our studies showed that the informant was an important factor predicting how the women experienced the information, where information communicated by someone with specialization in pediatric cardiology was significantly more often experienced as sufficient and understood by the women. The serial Doppler/echocardiography examinations did not induce anxiety, but rather coming to a highly specialized center and getting the possibility to interact and to get information and support from the staff was experienced as a benefit by the women. Women giving birth to a child with CHB often wished for more support. When investigating neurodevelopment, our data indicate that in addition to well established factors such as male sex and being born preterm, both maternal systemic lupus erythematosus (SLE) and CHB may influence neurodevelopment.

In conclusion, the result from this study highlights the vulnerable situation that women and their families experience when there is a risk for the child to develop CHB. We conclude that it is important to develop structured programmes for the surveillance of pregnancy in women who are SSA/Ro52 positive and to refer these women to specialized centers where the experience to manage the situation and with the possibility of maintaining updated information, surveillance and treatment is available. Such programme should also include guidelines for the involved personnel in the chain of care and make relevant information accessible for the women/families. Offering professional psychological support to the women and families should also be considered. In particular, for the women that gave birth to a child with CHB, the surveillance programme should range into the post partum period, and also involve the primary child care center to bridge the gap between different care givers. In addition, follow up of neurodevelopment should be considered for children with CHB, especially if the mother is diagnosed with SLE. An early diagnosis is one way to help these children overcome their difficulties during childhood and school years and make sure that they obtain the support needed.

*Två sanningar närmar sig varann.
En kommer inifrån,
en kommer utifrån
och där de möts har man en chans att få se sig själv.*

Tomas Tranströmer

LIST OF PUBLICATIONS

The thesis is based on the following papers which will be referred to with their Roman numerals in the text.

- I. **Tingström J**, Barimani M, Sonesson S-E, Wahren-Herlenius M, Welin Henriksson E. **The Experiences of Pregnancy in Women with SSA/Ro52 autoantibodies.** *Musculoskeletal Care.* 2010 Dec;8(4):215-23
- II. **Tingström J**, Welin Henriksson E, Sonesson S-E, Wahren-Herlenius M. **Ro52 autoantibody-positive women's experience of being pregnant and giving birth to a child with congenital heart block.** *Midwifery.* 2013 Jan;29(1):18-23.
- III. **Tingström J**, Hjelmstedt A, Welin Henriksson E, Sonesson S-E, Wahren-Herlenius M. **Ro52 autoantibody-positive risk pregnancy: Reactions induced by serial Doppler examination surveillance.** *Manuscript*
- IV. **Tingström J**, Hjelmstedt A, Welin Henriksson E, Sonesson S-E, Wahren-Herlenius M. **Ro/ SSA autoantibody mediated congenital heart block indicate need for increased information, support and highly specialized medical care.** *Manuscript*
- V. **Tingström J**, Källberg H, Hjelmstedt A, Welin Henriksson E, Sonesson S-E, Wahren-Herlenius M. **Ro52 autoantibody-positive women's experiences after childbirth, with or without a child with congenital heart block.** *Manuscript*
- VI. Skog A, **Tingström J**, Salomonsson S, Sonesson S-E, Wahren-Herlenius M. **Neurodevelopment in children with and without congenital heart block born to anti-Ro/SSA-positive mothers.** *Acta Paed.* 2013 Jan; 102(1):40-46.

RELATED PAPERS NOT INCLUDED IN THE THESIS

- I. Ambrosi A, Salomonsson S, Eliasson H, Zeffner E, Skog A, Dzikaite V, Bergman G, Fernlund E, **Tingström J**, Theander E, Rydberg A, Skogh T, Öhman A, Lundström U, Mellander M, Winqvist O, Fored M, Ekbohm A, Alfredsson L, Källberg H, Olsson T, Gadler F, Jonzon A, Kockum I, Sonesson SE, Wahren-Herlenius M
Development of heart block in children of SSA/SSB-autoantibody-positive women is associated with maternal age and displays a season-of-birth pattern.
Ann Rheum Dis. 2012 Mar;71(3):334-40.

- II. Skog A, Eliasson H, **Tingström J**, Källberg H, Salomonsson S; The Swedish Congenital Heart Block Study Group, Sonesson SE, Wahren-Herlenius M.
Long-term growth of children with autoantibody-mediated congenital heart block.
Acta Paediatr. 2013 Mar 28. [Epub ahead of print]

TABLE OF CONTENTS

1	INTRODUCTION	11
1.1	Pregnancy	11
1.1.1	Transition to motherhood and preparation of parenthood	11
1.1.2	Ultrasound during pregnancy	11
1.2	High- risk pregnancy	12
1.3	Pregnancy complications in systemic rheumatic disorders.....	13
1.3.1	The immune system during pregnancy	13
1.3.2	Systemic lupus erythematosus and Sjögren’s syndrome	13
1.4	Autoimmunity to Ro/SSA and La/SSB Proteins.....	15
1.5	Neonatal Lupus Erythematosus (NLE).....	17
1.5.1	Cutaneous lesions.....	17
1.5.2	Liver and hematological complications.....	18
1.5.3	Other complications including neurological involvement.....	18
1.6	Congenital heart block (CHB)	19
1.6.1	Atrio ventricular block I, II and III.....	20
1.7	Clinical aspects of Congenital Heart Block.....	22
1.7.1	Incidence	22
1.7.2	Morbidity and mortality.....	23
1.7.3	Surveillance and treatment of CHB during pregnancy	23
2	AIMS OF THE STUDY:	26
3	PATIENTS AND METHODS - CONSIDERATIONS	27
3.1	Participants	27
3.1.1	Doppler group	28
3.1.2	CHB group	28
3.1.3	Neurodevelopmental follow-up.....	29
3.2	Methods	31
3.2.1	Qualitative research method	31
3.2.2	Quantitative research methods.....	32
3.3	Time span	34
3.4	Ethical consideration	34
4	RESULTS AND DISCUSSION.....	36
4.1	THESIS STRUCTURE AND WORKFLOW.....	36
4.1.1	Interviews, paper I and II.....	36
4.1.2	Questionnaires, paper III, IV, V and VI.....	38
4.1.3	Medical records, paper VI.....	42
4.2	INFORMATION.....	42
4.2.1	Healthcare interactions.....	42
4.2.2	Self-sought information	48
4.2.3	Information - Summary.....	48
4.3	EMOTIONAL RESPONSE IN Ro/SSA POSITIVE PREGNANCIES	49
4.3.1	Feeling safe or not, in an uncertain situation.....	49
4.3.2	Feelings of concern and anxiety	51
4.3.3	Suspense and “on hold”	51
4.3.4	Feelings of guilt.....	52
4.3.5	Thoughts about determination	53
4.3.6	Emotional response - Summary.....	53
4.4	SUPPORT.....	53
4.4.1	Given support	53

4.4.2	Desired support.....	55
4.4.3	Support - Summary	56
4.4.4	ORGANIZATION OF CARE AROUND Ro/SSA POSITIVE PREGNANCIES.....	56
4.4.5	Primary care and specialized centers	56
4.4.6	Involved clinics and their coordination	56
4.4.7	Doppler examinations	57
4.4.8	Organization - Summary	57
4.5	LOSING THE CHILD IN UTERO OR IN CONNECTION WITH BIRTH	58
4.6	THE POSTNATAL PERIOD	58
4.6.1	At the hospital.....	58
4.6.2	Coming home with a child with or without CHB	59
4.6.3	Child health care centers	59
4.6.4	Networking	59
4.6.5	Future perspective for the individual	60
4.6.6	Postnatal period - Summary	60
4.7	OTHER FAMILY MEMBERS	61
4.7.1	FOLLOW UP OF CHILDREN WITH CHB AND THEIR SIBLINGS (paper VI)	61
4.7.2	Follow up - Summary.....	62
5	CONCLUDING REMARKS.....	63
6	ACKNOWLEDGEMENTS.....	65
7	REFERECES	68

List of abbreviations

APL	Antiphospholipid syndrome
AV	Atrioventricular
AVB	Atrioventricular block
Bpm	Beats per minute
CHB	Congenital heart block
ECG	Electrocardiography
GA	Gestational age
GW	Gestational week
IVIG	Intravenous immunoglobulin
kD	Kilo Dalton
NLE	Neonatal lupus erythematosus
pSS	Primary Sjögren's Syndrome
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome

1 INTRODUCTION

1.1 PREGNANCY

1.1.1 Transition to motherhood and preparation of parenthood

Pregnancy is a time of transition in a woman's life, characterized by psychological processes and biological changes. Transitions are times of change, vulnerability, and transformation (Meleis et al., 2000). The transition to parenthood is a major life change that requires ability to adapt to a previously unknown situation and self-redefinition is needed to take on the maternal role (Mercer, 2004). A characteristic of the parenthood transition is that it takes place during an undefined period of time, with new life goals including ensuring the infant's survival and letting the infant become the primary focus of attention (Stern, 1998).

The mental and psychological preparation for parenthood may start a long time before the pregnancy, but increases during pregnancy (Condon, 1997; Hjelmstedt et al., 2006; Leifer, 1977). Fantasies about the child and what life will be like as a family, as well as increased emotional sense have been suggested to contribute to the preparation for parenthood (Stern and Bruschiweiler-Stern, 1998). During pregnancy, particular events such as feeling the fetal movements or seeing the fetus during an ultrasound exam seem to improve prenatal attachment (Ekelin et al., 2004; Kowalcek et al., 2003b). The engagement in the fetus during pregnancy has also been suggested to predict engagement in the infant after birth (Figueiredo and Costa, 2009; Siddiqui and Hägglöf, 2000). The early mother-infant relationship is of critical importance, because it forms the basis for the child's future social and cognitive development. Maternal behaviors such as sensitivity, acceptance and co-operation have been associated with the establishment and maintenance of a positive relationship with her infant (Ainsworth, 1979).

1.1.2 Ultrasound during pregnancy

Fetal diagnostics is the generic term for the examinations, screening and diagnostic examinations that can be performed during pregnancy. By using different techniques it is possible to detect and exclude certain diseases and injuries but it is never a guarantee for a healthy child (Georgsson Ohman et al., 2004). The ultrasound examination has become an almost universal part of antenatal care in developed countries (Garcia et al., 2002). Ultrasound examinations during pregnancy were introduced in Sweden in 1973. This non-invasive technique is now used for fetal diagnostics and offered as a routine procedure accepted in 97% of all pregnancies (Marsal and Malcus, 2008) predominantly in the second trimester (gestational

week 16-20) It is organized within the National Health Care System, and the primary medical indication to perform the examination is confirmation of gestational age, localization of the placenta and the detection of a multiple pregnancy (SBU, 2006).

The reasons for the women and their partners for undertaking the examination can be different and have been explored in several studies (Gudex et al., 2006; Lalor and Devane, 2007; Larsen et al., 2000). The reasons for an ultrasound examination are to know whether the child has malformations or if a multiple pregnancy exists (Ekelin et al., 2004; Gudex et al., 2006; Lalor and Devane, 2007; Larsen et al., 2000) Other reasons can be the need for reassurance, confirmation of a new life and looking at their child as a way of connecting with their child and “becoming a family” for the first time and parents are therefore often not prepared for anomalies if detected (Crang-Svalenius et al., 1996; Eurenus et al., 1997; Garcia et al., 2002; Kowalcek et al., 2003a; Molander et al., 2010).. As the ultrasound technique has developed, it has become possible to detect a variety of malformations, including congenital heart defects such as congenital heart block (CHB) during the second trimester (Paladini et al., 1993). One technique to investigate the blood flow and circulation in for example the placenta and the umbilical cord or to look at the conduction in the fetal heart is the Doppler/ ultrasound examination.

1.2 HIGH- RISK PREGNANCY

The definition of a high risk pregnancy is “an increased risk of mortality and morbidity due to fetal, maternal or placental defects” (O'Brien et al., 2010). The high risk definition is used to indicate that physiological, psychological, individual and/or environmental factors exist during pregnancy that can be a risk for the maternal and/or fetal health. In general women with a high risk pregnancy will experience more anxiety than women with a normal pregnancy (Gupton et al., 2001). Just the fact to be labeled as “high-risk” may cause fragility and physical vulnerability (McCain and Deatruck, 1994). Women being at risk during pregnancy have stated that they sometimes put their pregnancy “on hold” when being in a risk period (Ahman et al., 2010; Carolan and Hodnett, 2009). To struggle to come to terms with a situation when the fetal health is at risk, has been described as “trying not to be pregnant” as the women await the findings of genetic testing (Georgsson Ohman et al., 2004). In the study by Carolan and colleague 2009, participants expressed that they hold back their feelings of anticipation and excitement, and that they distanced themselves from the unborn baby (Carolan and Hodnett, 2009). This has also been described as a state of suspended investment in pregnancy related to

concerns around fetal abnormality (Carolan, 2005; Georgsson Ohman et al., 2004). It has been suggested that a poor prenatal engagement in the fetus is a predictor for poor engagement in the infant postpartum (Siddiqui and Hägglöf, 2000).

High-risk pregnancies require more medical monitoring which can be perceived as a less humanized care from the woman's perspective, where technical equipment and advanced medical tests receive a central role. There is also a special situation from the clinicians' perspective when caring for a high-risk pregnant woman. In a study from 2010, Pozzo et al found that 76% of the involved staff at a high-risk pregnancy clinic had difficulty in relating to and communicating with the patients (Pozzo et al., 2010).

1.3 PREGNANCY COMPLICATIONS IN SYSTEMIC RHEUMATIC DISORDERS

1.3.1 The immune system during pregnancy

A pregnancy involves physiological and hormonal changes for the woman. The maternal immune system is regulated to accept and not reject the fetus, a process in which the placenta is central. Dysfunction of the immune balance may result in e.g. preeclampsia (Matthiesen et al., 2005). Further, immune related rheumatic disease may deteriorate or even develop during pregnancy. For women who suffer from systemic rheumatic disorders the condition can influence reproduction and there is an increased risk of adverse outcome such as repeated fetal loss, intrauterine growth restriction and preterm birth (Märker-Hermann and Fischer-Betz, 2010; Tincani et al., 2006).

1.3.2 Systemic lupus erythematosus and Sjögren's syndrome

Systemic Lupus Erythematosus (SLE) and primary Sjögren's Syndrome (pSS) are both autoimmune inflammatory rheumatic diseases characterized by B cell hyperactivity and presence of autoantibodies. While pSS commonly affects exocrine glands with lymphocytic infiltrates and progressive tissue destruction (Jonsson et al., 2000), SLE is a more severe disease involving many organs and is characterized by the deposition of immune complexes, especially in the kidneys, joints, skin and blood vessels leading to glomerulonephritis, arthritis, skin rash and vasculities (Klippel, 1997).

Today, women with inflammatory rheumatic diseases can be encouraged to become pregnant, when there is a stable and quiescent phase of the disease. When the pregnant woman have a rheumatic diagnosis it is important to carefully and accurately penetrate the anamnesis in

order to understand disease activity and define parameters that may influence the pregnancy. Sjögren's syndrome may affect women of all ages but is most frequent between 40-50 years of age. However, early-onset of primary Sjögren's Syndrome is usually associated with more systemic disease complications and high concentrations of autoantibodies (Hussein et al., 2011; Ramos-Casals et al., 2008). The study by Hussein and colleagues from 2011 showed that maternal age was higher in pSS patients, birth weight in pSS offspring lower and delivery by Caesarean section or vacuum extraction more frequent than in the general population. The increased risk for surgical delivery is mainly due to an increased risk of fetal growth restriction in the pSS pregnancies, resulting in increased risk of severe fetal outcome.

The onset of SLE often occurs when a woman is in her fertile years, and pregnancy and its outcome is a major concern of most SLE patients. It is important that a woman with SLE and her partner who wants to become parents discuss their wish and various aspects of pregnancy with a rheumatologist. Whether there is an increased risk of SLE flares during pregnancy remains controversial. As a general rule, the longer a patient has been in remission at the time of conception, the higher is the chance that she can complete the pregnancy without experiencing a disease exacerbation (Mok and Wong, 2001). The risk of a miscarriage during an SLE-pregnancy is 20-40% and the risk for premature birth (<37 GW) is around 40% (Skomsvoll et al., 1998). One of the reasons for the increased risk is the presence of anti-phospholipids antibodies (APL), which has been found in SLE patients. APL have been shown to cause intra-placental thrombosis, leading to placental insufficiency and miscarriages, usually in the second and third trimester (Ginsberg et al., 1992; Tincani et al., 1998).

Differentiation between pre-eclampsia and flare of SLE during pregnancy can be difficult. Both conditions can cause hypertension, protein urea, oedema and deteriorating renal function, and all symptoms may be present in the same patient. A distinction between the two conditions is however important because the management is different (Buyon and Szer, 1986; Petri, 1998).

SLE and pSS are partly overlapping diseases, and patients with both diagnoses may be positive for SSA/SSB autoantibodies. The risk of fetal loss in pSS was reported as similar to that in women with SLE (Julkunen et al., 1995). Larger studies are however needed to understand the underlying causes and mechanisms behind outcome factors in pregnancy in pSS patients. Today, it is likely that most women with rheumatic diagnoses will complete their pregnancy without serious complications for the mother or child thanks to the combined efforts from different specialist care-givers. It is important that involved health care professionals work

together as a team and at the same time interdependently, since no discipline of the team has the complete skill or knowledge required to care for the complex maternal-fetal relation (Handley and Collins, 2008; Saar et al., 2006).

1.4 AUTOIMMUNITY TO Ro/SSA AND La/SSB PROTEINS

Recent data show that subspecificities of Ro52 autoantibodies induce congenital heart block (CHB) (Ambrosi and Wahren-Herlenius, 2012; Salomonsson et al., 2005). Based on this observation immune-serologic assays have been developed that allow identification of high risk pregnancies with respect to CHB (Strandberg et al., 2010). These pregnancies can then be monitored by Doppler/echocardiography surveillance during susceptibility weeks 18-24. Below follows a short description of the Ro and La antigens, the detailed understanding of which enabled the identification of the pathogenic Ro/SSA autoantibodies.

Patients with SLE and SS often have autoantibodies against Ro/SSA and La/SSB. The Ro/SSA antigen refers to two non-homologues proteins, the 52 kilo Dalton (kD) protein Ro52 and the 60 kD protein Ro60. Ro52 contains a RING and a B-box, a coiled-coil domain and is expressed mostly in immune-related organs and cells. Ro52 is expressed in immune cells and is mainly localized in the cell cytoplasm but can translocate into the nucleus upon inflammatory stimuli. The biological function of Ro52 is as a RING-dependent E3 ligase involved in ubiquitination and regulation of immune responses (Espinosa et al., 2009; Espinosa et al., 2006).

The RING, B-box and coiled coil motif places Ro52 in the family of tripartite motif proteins, TRIMs (Reymond et al., 2001). Many of the TRIM proteins Ro52 has been shown to have E3 ligase activity and acts in the ubiquitination process (Espinosa et al., 2006). The ubiquitination is a mechanism of post-translational modification of proteins that allows cells to control biological processes such as protein degradation, trafficking and activation (Hershko et al., 1983). Many of the proteins in the TRIM family play an important role in innate immunity and antiviral responses (Nisole et al., 2005), but also in the regulation of immune responses by targeting molecules involved in the cell proliferation, survival and death (McNab et al., 2011). The term Ro52 is commonly used when discussing autoantibodies in the clinical situation, but as a TRIM protein Ro52 is also called TRIM21, which is the formal name of the Ro52 gene (Reymond et al., 2001).

When the maternal autoantibodies to Ro52, Ro60 or La are passively transported cross the placenta during pregnancy they can injure the previously normal fetal heart

(Franceschini and Cavazzana, 2005; Wahren et al., 1996). Autoantibodies targeting the 52-kDa component of the Ro antigen are the antibodies most closely associated with CHB. In vitro experiments and animal models of CHB also point to a major role for anti-Ro52 antibodies targeting amino acids 200-239 in CHB pathogenesis, and suggest that these might directly bind cardiomyocytes and affect calcium regulation in the fetal heart, leading to disturbances in signal conduction or electro genesis or both (Ambrosi and Wahren-Herlenius, 2012). As reviewed by Wolin et al (Wolin and Reinisch, 2006), Ro60 is a ubiquitously expressed RNA-binding protein shaped like a doughnut with an inner hole. In the cell, Ro60 binds a family of small cytoplasmic RNAs, hYRNA 1-5. While the function of Ro60 was unknown for many years, experiments have now demonstrated that this protein binds misfolded non-coding RNAs in vertebrate cells and likely functions in a pathway by which defective RNAs are recognized and targeted for degradation (Chen et al., 2003; Labbé et al., 1999; O'Brien and Wolin, 1994). It has also been shown that the Ro60 protein is important for cell survival after ultraviolet irradiation (Chen et al., 2000; Chen et al., 2003). The La protein can also associate with the hYRNAs and has been suggested to have a function in transcription termination and may also be involved in virus replication (Wolin and Cedervall, 2002). Notably, while antibodies towards Ro52 seem to be the major link to CHB, Ro60 and La autoantibodies may amplify the pathogenic cascade and bind intracellular proteins exposed on the cell surface during apoptosis (Ambrosi and Wahren-Herlenius, 2012).

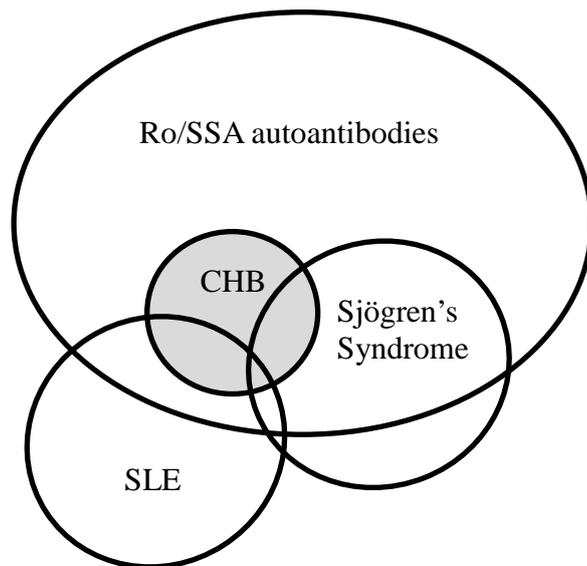


Figure 1. Relation of CHB to maternal diagnosis and autoantibody positivity. The mothers of children with CHB may be diagnosed with SLE or Sjögren's syndrome, but may also be carriers of Ro/SSA autoantibodies without any clinical manifestations of rheumatic disease.

1.5 NEONATAL LUPUS ERYTHEMATOSUS (NLE)

Neonatal lupus erythematosus (NLE) occurs in children born to mothers with antibodies to SSA/Ro and/or SSB/La. The mothers are often diagnosed with SLE or Sjögren's syndrome. However, many cases also occur in infants of mothers who have the autoantibodies, but who do not have symptoms of lupus or other autoimmune disease at the time of pregnancy or delivery. Neonatal lupus includes several clinical manifestations as described below.

1.5.1 Cutaneous lesions

One of the most common manifestations of NLE is cutaneous lesions (Buyon and Clancy, 2003). NLE has been reported to occur in 15-25% of infants exposed to SSA/Ro antibodies in utero, but the true incidence is unknown since it is probably underreported and mistaken for other neonatal rashes (Lee and Weston, 1997). The lesions are often seen in the face but can also be found on the trunk, diaper area or extremities (Weston et al., 1999). The skin lesions are photosensitive but can occur even if not sun exposed (Friedman et al., 2002; Lee, 2010; Neiman et al., 2000).



Figure 2. Photograph of a newborn infant with cutaneous NLE lesions. From: J Invest Dermatol Symp Proc 2011.

1.5.2 Liver and hematological complications

Liver involvement connected to NLE is often asymptomatic and seen in elevated liver function tests, such as alanine aminotransferase and or aspartate aminotransferase (Silverman and Jaeggi, 2010). Hematological disorders, such as anemia and thrombocytopenia, also occur, but less frequently (Selander et al., 1998; Wolach et al., 1993). Mostly the infants do not display any clinical symptoms but in a study by Cimaz and colleagues where 120 infants who had been exposed to anti-SSA/Ro antibodies were followed, 26% had at least one liver test abnormality (Cimaz et al., 2003). Symptoms of liver dysfunction or a hematological disorder are transient and will resolve as maternal autoantibodies are cleared from the child's circulation at approximately 6-8 months of age (Friedman 2002, Lee 2009). Breastfeeding, which theoretically prolongs the exposure of the infant to maternal autoantibodies, does not appear to influence the development of NLE skin lesions (Askanase 2002, Klauninger et al 2009). If a child to a mother with anti-SSA/Ro antibodies shows no signs of NLE, screening for hematologic, hepatic or neurologic changes is not recommended. If, however, the infant becomes ill, the risk of NLE should be taken in consideration (Wahren Herlenius et al., 2012).

1.5.3 Other complications including neurological involvement

Beside the cutaneous, liver and hematological involvement, NLE has also been suggested to involve neurologic manifestations. Nakayama-Furukawa and colleagues described two cases of hydrocephalus connected to NLE (Nakayama-Furukawa et al., 1994). A study that prospectively examined 87 infants born to mothers with Ro/SSA autoantibodies 8% of the children had hydrocephalus, concluding that hydrocephalus should be considered as a new

manifestation of NLE (Boros et al., 2007). When combining CT scan and ultrasounds on infants with coetaneous NLE mild abnormalities were found. The most frequent findings were non-specific white matter changes and calcification of the basal ganglia. Rare cases of macrocephaly, vasculopathy and transient myasthenia gravis are also found (Cabanas et al., 1996; Kaye et al., 1987). Another rare condition related to CHB is Chondrodysplasia punctata, characterized by radiographic stippling of the epiphyses and/or spine. In general, it resolves without treatment during childhood, within the first year. Through the years more than 15 cases of Chondrodysplasia punctata have been associated with maternal autoantibodies and it is therefore likely that it is a skeletal manifestation of NLE (Austin-Ward et al., 1998; Chitayat et al., 2008; Elcioglu and Hall, 1998; Honda et al., 2008; Kelly et al., 1999; Kozlowski et al., 2004; Shanske et al., 2007).

The blood-brain barrier is not completely formed in utero, leading to potential exposure of the fetal nervous system to maternal Ro/SSA autoantibodies. Askanase and colleagues observed an increased frequency of attention-deficit disorder in boys with CHB (Askanase et al., 2010). It has also been reported that there might be a higher prevalence of learning disabilities and attention-deficit disorders in boys of mothers with SLE (Neri et al., 2004; Ross et al., 2003). Further studies would contribute to better understanding of this complex situation and ensure that the children and families that are involved get adequate surveillance and support during pregnancy, growth and school years.

A serious feature of NLE is the cardiac involvement, which includes arrhythmias and different stages of atrio ventricular (AV) block (Friedman et al., 2003; Lee, 2009) which is described more detailed below.

1.6 CONGENITAL HEART BLOCK (CHB)

Heart block that develops during fetal life, CHB, is most commonly associated with either congenital malformations or the presence of Ro52, Ro60/La autoantibodies in the mother. Sometimes the heart block may occur after viral infections, drug treatment or can be diagnosed without any identifiable cause. Heart block may also develop during infancy or early childhood. To distinguish true CHB cases from heart blocks developed later in life a new definition of CHB has been proposed; heart block is considered as congenital if it is diagnosed during pregnancy, in utero, or within the neonatal period (0-27 days of life) (Brucato et al., 2003). These heart blocks are potentially fatal conditions with conduction abnormalities in a structurally normal heart (Buyon and Clancy, 2003).

The congenital heart block observed in NLE usually develops during gestational week (GW) 18-24. The maternal Ro/SSA and La/SSB autoantibodies are transported from the mother to the fetus across the placenta during pregnancy. Maternal anti-Ro52 antibodies are directly connected to the development of CHB, although the molecular mechanisms are still to be unraveled (Salomonsson et al., 2002). Further, since the recurrence rate is only 12-17% (Ambrosi and Wahren-Herlenius, 2012; Buyon et al., 1998; Julkunen and Eronen, 2001; Solomon et al., 2003) despite persisting maternal autoantibodies, other factors besides antibodies are needed for the full establishment of CHB.

1.6.1 Atrio ventricular block I, II and III

CHB is defined as a block or a delay in the signal conduction at the AV node and can be divided in three degrees of severity. The process may be initiated as a first degree block and can progress through second degree and eventually to a complete third degree block (Bergman et al., 2009; Clancy and Buyon, 2004; Litsey et al., 1985). In first-degree AVB (AVB I), the electrical impulses are slowed down as they pass through the AV node. AVB I is characterized by a prolonged interval between atrial and ventricular contractions (AV interval) but with normal and atrial and ventricular rates (Jaeggi and Nii, 2005).

In second degree AV block (AVB II), some, but not all, impulses reach the ventricles. AV block II exists as three different types. Mobitz type I, with a progressive prolongation of the AV conduction, Mobitz type II with block of an isolated impulse without lengthening of the AV conduction time, and 2:1 second degree AV-block which is characterized by blocking every second atrial impulse. A third degree, complete heart block, (AVB III) occurs when no signals are conducted through the AV node. This results in a low ventricular rate, bradycardia, usually between 50-70 beats per minute (bpm) while the atrial rates are usually normal, (110-150 bpm). AVB I and AVB II are both considered as reversible but AVB III in CHB is considered to be permanent and usually results in need for a pacemaker after birth (Eronen et al., 2000; Sonesson et al., 2004; Waltuck and Buyon, 1994). Lately, a publication of reverting AVB III has however challenged the permanency of the third-degree block (Trucco et al., 2011).

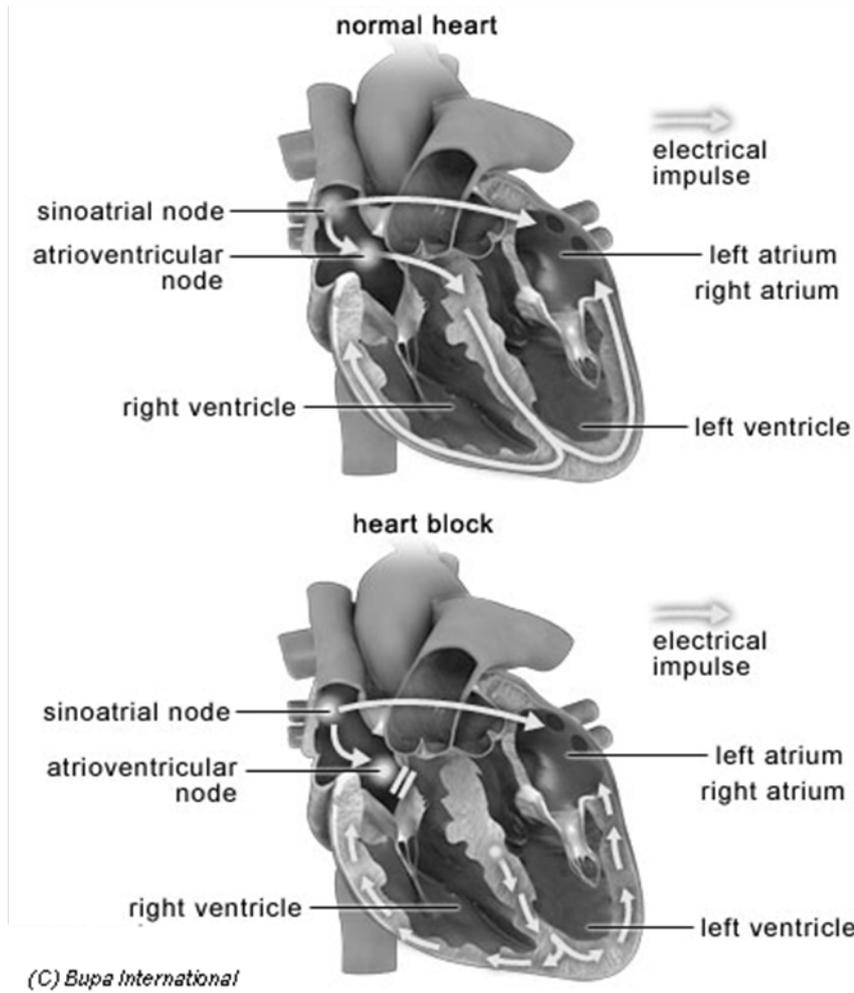


Figure 3. The electrical impulses in a normal heart and a heart with heart block.

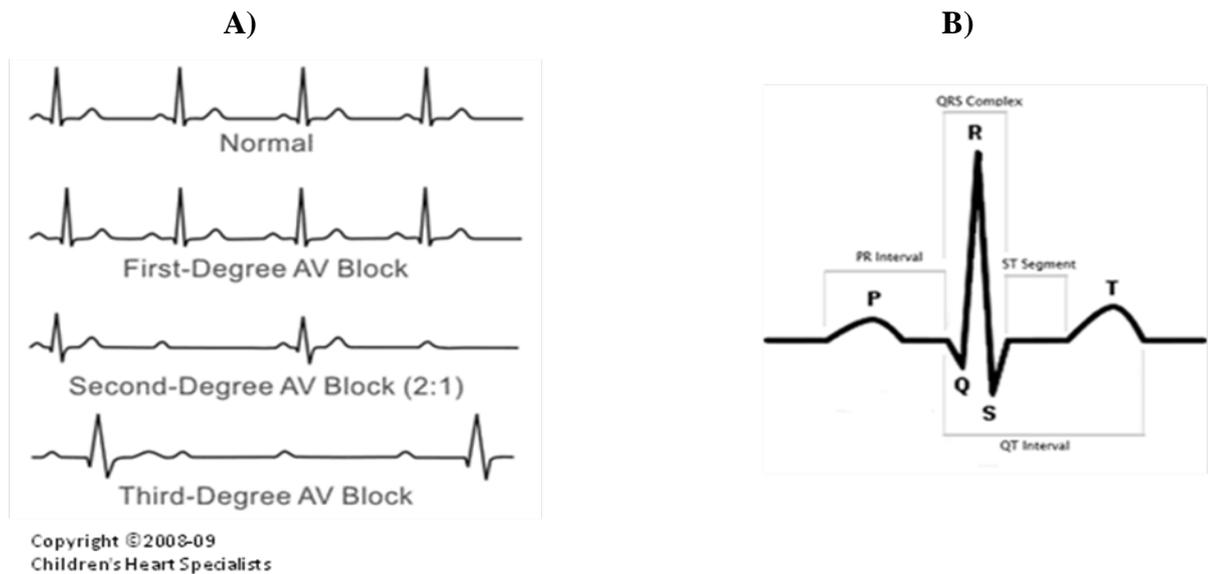


Figure 4.

(A) ECG showing normal sinus rhythm, first, second and third-degree AV-block.

(B) A schematic picture of a normal ECG curve. The PR interval is measured from the start of the p-wave (depolarization of the atria) to the beginning of the QRS complex (depolarization of the ventricles).

1.7 CLINICAL ASPECTS OF CONGENITAL HEART BLOCK

1.7.1 Incidence

CHB is a rare disease with an incidence in newborn children of 1/15.000-20.000 in the general population (Michaelsson and Engle, 1972). The prevalence of having a child with a third-degree block is about 1-2% in women positive for Ro/SSA autoantibodies (Brucato et al., 2001; Buyon et al., 2001; Friedman et al., 2002). If the maternal anti-Ro activity is targeted to the 52-kd component of the Ro antigen, it has been suggested to be even more frequent (Buyon et al., 1993; Julkunen et al., 1998; Salomonsson et al., 2002). In cases where the mother previously gave birth to a child with CHB the recurrence rate is 12-17% (Buyon et al., 1998; Julkunen and Eronen, 2001; Llanos et al., 2009; Solomon et al., 2003). If the mother previously had a child with NLE involving the skin the occurrence of cardiac involvement has been reported to be 13% in the next child (Izmirly et al., 2011). The incidence for AVB I in Ro/SSA positive pregnancies range from 9 % to 33% depending on cut-off values employed for defining the AVB I (Bergman et al., 2009; Friedman et al., 2008; Rein et al., 2009; Sonesson et al., 2004).

The first sign of a mother being Ro/SSA autoantibody positive can be that the fetus shows signs of heart block. As these mothers are not aware of their autoantibodies, offering fetal surveillance during pregnancy will not be possible unless a general screen of Ro/SSA autoantibodies in early pregnancy is introduced. It also indicates that the fetus is very sensitive to the maternal biosystem.

1.7.2 Morbidity and mortality

CHB has a mortality of 15-30% (Buyon et al., 1998; Jaeggi et al., 2002; Schmidt et al., 1991; Waltuck and Buyon, 1994). The outcome for patients with congenital heart block depends on the presence or absence of underlying structural heart disease, as well as the rate of ventricular activation and the presence or absence of congestive heart failure (Friedman et al., 2003). If the heart rate is lower than 55 beats per minute (bpm) during the fetal period there is a high risk of fetal loss (Jaeggi et al., 2002). The presence of fetal hydrops or other signs of physiologic disturbance in cardiac function are also poor prognostic signs (Friedman et al., 2003). If the congenital heart block is diagnosed in the newborn period (0-27 days of life), and structurally normal, the condition is associated with a very good prognosis for long-term survival (Buyon et al., 1998; Eliasson et al., 2011). The majority of the surviving children need a pacemaker in early life (Buyon et al., 1998; Eronen et al., 2000; Waltuck and Buyon, 1994).

1.7.3 Surveillance and treatment of CHB during pregnancy

Fetal echocardiographic and Doppler methods are the dominating modality for prenatal diagnosis of fetal cardiac rhythm, conduction, and function. Advances in signal processing have improved the acquisition of transabdominal fetal electrocardiography (ECG), but atrial depolarization's (p waves) are still difficult to detect. Another technique to follow the development of the fetal heart is magnetocardiography. This technique provides a better quality of the signal than ECG, but it is expensive and requires a magnetically shielded room. The technique is available in a few centers, but not in Sweden. Assuming that CHB is a gradually progressing and preventable disease, starting during a critical period in mid gestation, methods to detect first degree heart block have been developed. By monitoring the development of the fetal heart during GW 18-24 a correct diagnosis can be made (Andelfinger et al., 2001; Bergman et al., 2006; Sonesson, 2010).

Ultrasound Doppler methods have been developed with reference values established to detect first-degree atrioventricular block (AVB) (Andelfinger et al., 2001; Glickstein et al.,

2000). It has been shown that signs of first degree heart block occur in up to 1/3 of fetuses of autoantibody positive women (Sonesson et al., 2004). These blocks revert spontaneously in the majority of the fetuses, but progression to a more severe block may occur in some. In these cases the surveillance may enable early treatment of the pathogenic process, and maybe reverse the inflammatory process in the fetal heart (Sonesson et al., 2004; Theander et al., 2001). Different ways to improve the outcome in fetuses with CHB, including anti-inflammatory treatment with steroids, (Bierman et al., 1988; Buyon et al., 1987; Saleeb et al., 1999) intravenous immune-globulins (IVIg) (Kaaja et al., 1993; Kaaja et al., 1991) and plasmapheresis (Makino et al., 2007; van der Leij et al., 1994) have been used.

Fluorinated steroids (betamethasone and dexametasone) are the most commonly used treatment. Steroids are used to reduce the inflammatory process in the fetal heart to avoid or decrease the injury in the fetal heart. Fluorinated steroids cross the placenta without being metabolized (Blanford and Murphy, 1977). Even if CHB is established, treatment with steroids might decrease the inflammation in the fetal heart and increase the fetal cardiac output. As a complement beta-sympathomimetics may be used (Hutter et al., 2010). Fluorinated steroids administered to non-complete AV block have been indicated to prevent progression or even revert the block (Buyon et al., 1995; Friedman et al., 2008; Rein et al., 2009; Rosenthal et al., 1998; Saleeb et al., 1999; Theander et al., 2001). However, the use of fluorinated steroids is connected with adverse effects for both mother and child. Main risks for the mother includes infection, hypertension, glucose intolerance, osteoporosis and preeclampsia. The main risk for the fetus includes oligohydramnios, growth restriction and risk for negative neurological development (Hutter et al., 2010) As mentioned above, other therapies can be used, although evidence based results of its efficacy is lacking The use of injection of immunoglobulin, IVIg was first assumed to block the maternal autoantibody transport to the fetus (Hutter et al., 2010), but other studies showed no benefit of the treatment in preventing complete AVB (Friedman et al., 2010; Pisoni et al., 2010). Using plasmapheresis treatment is a way intended to reduce maternal Ro/La autoantibodies in the maternal and thereby fetal circulation and in that way protect the fetal heart from damage, but the studies performed all combined the treatment with transplacental steroid treatment and its efficacy is therefore difficult to assess (Barclay et al., 1987; Buyon et al., 1987; Ruffatti et al., 2012; Saleeb et al., 1999). Since no studies at the moment are adequately powered to answer the question as to which management strategy of Ro/SSA positive pregnancies will result in the best prenatal and long time outcome (Cuneo et al., 2010), and there is no consensus among experts in how to best meet the challenge in this

complex situation, it is extremely important for the team that work with the family to adjust to each individual condition.

2 AIMS OF THE STUDY:

Congenital heart block may develop in the fetus of women with Ro/SSA autoantibodies. The potentially lethal autoantibody-mediated congenital heart block is rare, and studies investigating the experience of pregnancy in Ro/SSA autoantibody positive women are lacking. The overall aim of this thesis was to explore and understand Ro/SSA autoantibody positive women's experiences of pregnancy and the time thereafter, with the goal to identify potential areas for improvement in care and routines.

The thesis was structured into six studies of different character:

- Two initial interview-based qualitative studies aimed at acquiring an in-depth understanding of Ro/SSA autoantibody positive women's experience of pregnancy, and to generate hypotheses to be tested in larger groups of individuals (paper I and II).
- Three following studies aimed at testing the interviewed-derived hypotheses on information, emotional reactions, support, organization of care around Ro/SSA positive pregnancies and elements related to the postnatal period derived from the first interview studies (paper I, II) in larger groups of individuals using questionnaires (paper III, IV, V).
- An additional aim of the thesis was to investigate whether neurodevelopment in children born with CHB and their siblings differs from that of the general population, and if so, to define factors that might predict neurodevelopment aberrances (paper VI).

3 PATIENTS AND METHODS - CONSIDERATIONS

For a detailed description of patients and methods in this thesis, please see the methodological section in each of the included papers. In the following section methodological considerations will be discussed, including advantages and disadvantages of the chosen approaches.

In order to fulfill the overall aim for the thesis, data were acquired through both qualitative and quantitative research methods. The studies are summarized in Table 1, outlining the study design for each paper. The qualitative studies (paper I and II) are based on individual semi-structured interviews with one group of women who were at risk for having a child with CHB (Doppler group) and one group of women who did give birth to a child with CHB (CHB group). The quantitative studies in paper III-V and to some extent paper VI are based on a questionnaire which was constructed based on the results from paper I and II. Paper VI is mainly based on data extracted from medical records of the children born with CHB and their siblings. All women who participated in the studies were positive for Ro/SSA autoantibodies.

3.1 PARTICIPANTS

One challenge in studying CHB and situations related to CHB is that CHB is rare. In paper I and III we invited Ro/SSA positive women who had participated in the surveillance programme for detecting early signs of CHB at Astrid Lindgrens Hospital (Stockholm, Sweden) during gestational week (GW) 18-24 (Doppler group). The establishment of a population based cohort of Swedish congenital heart block (CHB) patients and their families (Salomonsson et al., 2011) has facilitated the study by identifying all known cases of CHB in Sweden, but the numbers of participants are still few compared to studies of many other diseases. In paper III and IV we invited identified mothers who had given birth to a child with CHB (CHB group). In paper V women from both groups participated (paper V, Table 1). The high percentage of participating mothers of index cases is strength, but there are also limitations. First, participants in paper IV and V are born within a long period of time, between 1929 and 1978. During this time a lot of routines have changed in the Swedish health care system and the knowledge about CHB and how to manage patients at risk has increased. Also the standard of keeping medical records during this time have changed and developed substantially. In paper VI individuals born 1974-2009 were included. Rules and regulations regarding keeping medical records within the primary health care and school health care have also developed over the years.

All the women in paper I and III participated in the same surveillance programme met the same nurses and doctors involved in the programme, and had the same information on the risk and diagnosis. The advantage is obviously the continuity but the disadvantage could be that if information or knowledge was missing, this could influence all participants. Another consideration is that the studies of the thesis were addressed only to the women/mothers. In a complicated situation when a fetus/child is at risk the partner and the whole family usually is involved and this has not fully been reflected or has been taken in consideration in this thesis. However, it should be pointed out that this is the first investigation where the experiences from Ro/SSA autoantibody positive women are studied and this work could be used as a starting point for future studies.

3.1.1 Doppler group

The women in the so called "Doppler group" are all Ro/SSA autoantibody positive. They were referred to the pediatric cardiology clinic at Astrid Lindgrens hospital at the Karolinska University Hospital between 1998 and 2010 to follow the development of the fetal heart during GW 18-24. None of the women in this group gave birth to a child with CHB. When the work with paper III started 100 mothers had undergone the surveillance programme and 79% agreed to participate (n=79) in paper III and V. A subgroup of these women were interviewed in paper I (n=14).

3.1.2 CHB group

Participants in the so called "CHB group" are all women who are Ro/SSA autoantibody positive and who gave birth to a child with CHB. They were identified through the population-based cohort of Swedish CHB patients described earlier by Salomonsson and colleagues (Salomonsson et al., 2011). When the work with paper IV started, 88 living mothers had been identified, and 89% agreed to participate (n=78) in paper IV and V. The children born with CHB were diagnosed at different time points. Depending on when the mother got the information on the child's diagnosis her experiences differed. In paper IV we therefore divided the mothers into two groups; diagnosis set in utero - *In utero* group, diagnosis set day 0-27 and later - *Post partum* group (paper IV, Figure 3A).

A subgroup of the women in the *In utero* group were interviewed in paper II (n=21).

3.1.3 Neurodevelopmental follow-up

In paper VI, data were extracted from medical records from children primary healthcare centers and school health services to retrieve data on impairment in the following categories of neurodevelopment; motor skill development, speech, attention, learning and behavior. Data on neuropsychiatric diagnoses were also retrieved. The children were identified through the populations based cohort of Swedish CHB patients described above. Medical records were collected from children with CHB (n=60) and their siblings without CHB (n=54) born 1974-2009 (n=114). An advantage of this study is the availability of the records, while a disadvantage is its retrospective character. A prospective study is however difficult to perform considering the rarity of the condition.

Table 1. Methods and studied participants of included papers.

Paper	Study area	Number of participants	Study group	Data collection method	Data analysis method
I	Women's description of being pregnant when SSA/Ro 52 autoantibody positive	n=14	Doppler	Semi structured interviews	Qualitative content analysis
III	Women's description of expecting a child with CHB	n=21	CHB	Semi structured interviews	Qualitative content analysis
IIII	Ro52 autoantibody-positive risk pregnancy and serial Doppler examinations	n=79	Doppler	Questionnaire	Descriptive statistics Fishers exact test
IV	The women's need when being pregnant with a child having autoantibody-mediated CHB	n=78	CHB	Questionnaire	Descriptive statistics Fishers exact test
V	Ro52 autoantibody positive women's experiences after childbirth	n=157	Doppler, CHB	Questionnaire	Descriptive statistics Fishers exact test Spearman correlation
VI	Neurodevelopment in children with and without congenital heart block born to anti-Ro/SSA positive mothers	n= 114	CHB- children, siblings	Medical records	The Chi-square test or the two-sided Fisher's exact test Logistic regression analysis

3.2 METHODS

3.2.1 Qualitative research method

3.2.1.1 *Semi structured interviews*

Paper I and II are based on semi-structured interviews. The semi structured interviews in this work were performed individually using an interview guide (Paper I). The questions were open-ended, with the main focus on letting the women describe feelings and situations that they had experienced during their pregnancy and post-partum period. The interview guide was produced through discussions within the research team and was tested in pilot interviews. To verify the readability, the members in the research group read the questions. One pilot interview was thereafter performed in the Doppler group and one in the CHB group, and after discussions and input the interview guide was slightly adjusted. Depending on the individual interviews, follow up questions were asked when clarification was needed. Suggestions and comments from the participants were encouraged in order to supplement information retrieved through the interview guide. The duration of the interviews was between 45-90 minutes. The interviews were performed based on the women's preferences for time point and location.

The interviewer in a semi-structured interview generally has a framework of themes to be explored. However, the specific topic or topics that the interviewer wants to explore during the interview are usually thought about well in advance. It is generally beneficial for interviewers to have an interview guide prepared. A semi-structured interview is flexible allowing new questions to be brought up during the interview depending on information contributed by what the interviewer says (Graneheim and Lundman, 2004). Interview guides can help researchers to focus the interview on the topics at hand without constraining them to a particular format. This freedom can help interviewers to tailor their questions to the people they are interviewing and to the context and situation. The disadvantage can be that the interview is focused around a special topic and that topics that the interviewed person would like to express can be missed. It is also possible that the interview is not as exploratory and in-depth as it would be if the interview was performed without an interview guide (Britten, 1995; Halcomb et al., 2006).

3.2.1.2 *Verbatim transcription*

All interviews in this thesis were transcribed verbatim. Names were replaced with a number during transcription. As a second step the transcriptions were read through word by word by JT while re-listening to the tape. Verbatim transcription of interview is often used in data management in analysis of verbal data (Halcomb et al., 2005).

3.2.1.3 *Qualitative content analysis*

After verbatim transcription of the interviews, qualitative content analysis was used as the method for analyzing the text generated from the interviews in paper I and II. The method can be used in an inductive and a deductive manner depending on the purpose of the study. In paper I and II an inductive approach (Elo and Kyngäs, 2008; Halcomb et al., 2006) was used due to the assumption that there are no previous studies dealing with how women experience being pregnant and Ro/SSA autoantibody positive. Qualitative research is by nature an interpretive process and therefore it is important that the researcher is unprejudiced (Byrne, 2001). The purpose with qualitative research is to understand and describe a specific situation (Byrne, 2001). Content analysis is a method that can be used with qualitative data (Elo and Kyngäs, 2008). With qualitative content analysis it is possible to systematically analyze text material such as semi structured interviews (Graneheim and Lundman, 2004). There are no simple guidelines and the results from the analysis depend on the investigator's skills and experiences. For the validity of the results the pre knowledge of the interviewer must be clearly stated and taken into consideration in the analysis process (Elo and Kyngäs, 2008).

3.2.2 *Quantitative research methods*

3.2.2.1 *Questionnaire*

Paper III, IV, V, and to some extent paper VI, are based on results from a questionnaire. The questionnaire was constructed based on results from the individual interviews in paper I and II. We developed the questionnaire in two parts. The first part (A) was generic for both groups (Doppler and CHB) and contained demographic questions such as year of birth, education, marital status, parity and country of origin and factors that may be related to risk for CHB, such as tobacco use and sun exposure. Questions concerning maternal health included rheumatic diagnosis, knowledge about autoantibodies, health problems related to the rheumatic diagnosis, other disease and treatment or medication if any. The second part (B) was tailored for the Doppler group and CHB group respectively, and consisted of questions focusing

mainly on feelings, situations and experiences during the pregnancy when expecting the child at risk. It was organized in themes regarding information, thoughts on the surveillance period and the pregnancy in general including emotional reactions, support, organization of care and elements related to the postnatal period. There were controlled case questions, statements to which the answer was given in a four-graded scale from *totally agree* to *totally disagree*, and open-ended questions to which specific comments could be added and space was provided for adding optional extra information. Again the research group first tested the readability and then the questionnaire was sent to participants in the Doppler group and the CHB group. Two questionnaires were tested by participants in the Doppler group and two by participants in the CHB group. After input they were slightly adjusted and the final version was distributed. The questionnaire was only available in Swedish.

3.2.2.1.1 *Open ended questions*

The questionnaire also contained open ended questions. The freely written answers could consist of only one word or a sentence or sometimes the answer could be a longer description up to one page. The method of using open questions was applied to capture free answers from the respondents, without any predefined alternative answers.

3.2.2.2 *Medical records*

Paper VI is mainly based on patient data and information extracted from medical records. In Sweden, children are followed systematically by nurses and doctors at local children primary healthcare between age 0-6 and school health services between 6-19 years of age. To collect clinical data on children with CHB and their sibling's medical records from child primary healthcare centers and school health care services were collected and used to retrieve data on the impairment in the following categories of neurodevelopment: motor skill development, speech, attention, learning and behavior. Data on neuropsychiatric diagnosis were also retrieved from the records. Supplementary information on maternal diagnosis and treatment during pregnancy was also retrieved from maternal medical records.

3.2.2.3 *Statistical analysis*

Data from the questionnaires were entered in to a MS Excel sheet. To examine the contingency between groups and significant associations the Chi square or Fisher's exact test when the expected frequency was <5 was applied. Logistic regression was used for predicting

the outcome of a dependent variable. All statistical analysis including frequency distribution was performed in Graph Pad Prism 5.01 for Windows.

3.3 TIME SPAN

A limitation of the studies in the theses is the temporal aspect. The time from a CHB pregnancy to participation in an interview or in the questionnaire study was often long and also differed substantially between subjects. Further, the time aspect differs between the two studied groups in that mothers in the CHB group were born 1924-1978 and experienced their pregnancies between 1958-2009, while the mothers of the Doppler group were born 1960-1987, and experienced their pregnancies 1999-2011. The interviews in paper I were only 14, and a reason for so few mothers accepting the invitation to participate in an interview could be that a long time had passed between the pregnancy and the invitation for the interview. It is possible that some women had left their experiences and thoughts behind them and that it was hard to recall the memories of experiences and procedures. However, memories from pregnancy and delivery are often described as well remembered by mothers (Simkin, 1991). The questionnaires were based on the interviewed mother's experiences. In this group they all gave birth to their children within a ten year period (1999-2009), and maybe the questions were designed in a way so that was harder to relate to the questions when there was a long time since the experienced pregnancy and childbirth. Extra space was however included in the questionnaire to encourage all participants to add extra information or share thoughts and experiences that was not included in the questionnaire.

3.4 ETHICAL CONSIDERATION

The participants in the thesis contributed according to their own free will. They were ensured confidentiality and were given written information before inclusion in any of the studies. The participants were informed that their contribution to this work was voluntary and if they choose to decline participation or withdraw from the study it would not interfere with their future care or contact with the hospital. No economic compensation was offered to the participants. However, if the interview took place outside the woman's home she was offered tea, coffee or a soft drink during the interview. None of the women who agreed to participate later withdraw. The participants in paper I and II pointed out the benefits of being able to talk thoroughly with someone about their experiences. For some of the participants this was the first time since the delivery.

Regarding paper VI the participants or parents of children included (if under 18 years of age) had all agreed to that clinical data could be obtained from medical records from hospital, child health care centers and school health services with written consent.

To ensure confidentiality, all names were removed before conducting any data analysis. Permission from the local ethics committee at Karolinska Institutet was obtained for all studies.

4 RESULTS AND DISCUSSION

The overall aim of this thesis was to explore and understand Ro/SSA autoantibody positive women's experiences of pregnancy and the time thereafter, with the goal to identify potential areas for improvement in care and routines. Since not all children to Ro/SSA autoantibody positive women develop heart block during pregnancy, but are at risk during GW 18-24 we invited both women who participated in a surveillance programme and gave birth to a child without heart block as well as women who gave birth to a child with CHB to participate. Below follows a description of the structure and workflow during the PhD period, and thereafter the results are discussed thematically.

4.1 THESIS STRUCTURE AND WORKFLOW

4.1.1 Interviews, paper I and II

To learn more and better understand how women experience pregnancy when being Ro/SSA-positive we invited women with this experience to participate in an individual semi-structured interview. All women who had participated in a surveillance programme during pregnancy, GW 18-24, at the Karolinska University Hospital in order to follow the development of the fetal heart and detect early signs of heart block were invited (paper I). At the time when the work with this thesis started 62 women had followed the programme during 1998-2008 and 14 women agreed to share their experiences. None of these mothers subsequently withdraw. How well these 14 women represent the full spectrum of experiences during pregnancy is difficult to assess. However, there was a more than 10 year spread in the age of the participating mothers, who also represented several different groups of rheumatic diagnoses and lived in many different parts of the country, arguing that the sample was still sized enough to uncover the spectrum of experiences during pregnancy in SSA/Ro52 positive pregnancy. It is possible that the participating mothers may represent a subgroup of individuals with more concerns than those who did not choose to participate, and it is therefore likely that this study does not underestimate the negative side of undergoing serial ultrasound/Doppler examinations with the purpose to detect deviating AV-time.

After verbatim transcription of the interviews we analyzed the text with qualitative content analysis as described above in section 3.2.1.4. The overall theme "Experience of a high risk pregnancy" emerged from the text with the categories information, emotional response and support, as shown below (Figure 5).

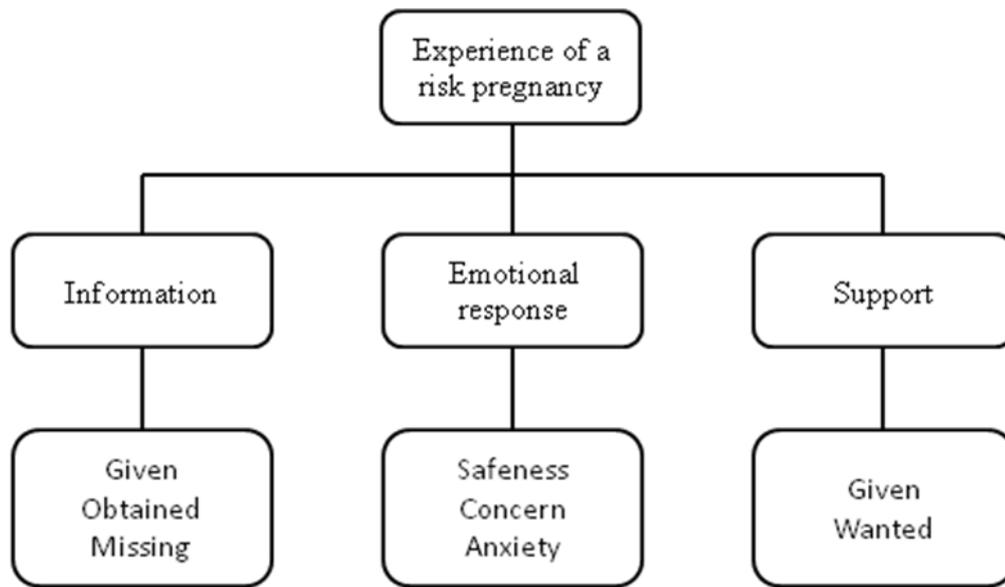


Figure 5. Description of theme categories and codes from paper I.

As a second step we invited all mothers who had been pregnant with a child with CHB during 2000-2009 (n=21), to an individual semi-structured interview (paper II). In three cases the child died in utero or shortly after birth. The 21 identified women of different ages and living in different parts of the country all agreed to participate, and interview results can thus be expected to represent the full spectrum of experiences during this period. None of the women subsequently withdraw. A drawback with the relatively long period for selecting cases is that for some of the women up to a decade had passed since the time of the CHB-related pregnancy, which might influence their memory of events and related emotions. However, we did not find any systematic differences between the responses obtained from such mothers and those from mothers with a more recent CHB-related pregnancy, and studies of traumatic memories indicate these are well remembered and reported with richness of details (Porter and Birt, 2001).

Again, qualitative content analysis was used to analyze the text after verbatim transcription. The overall theme was “Expecting a child with congenital heart block”. Three categories emerged from the responses: learning, suspense and facing (Figure 6).

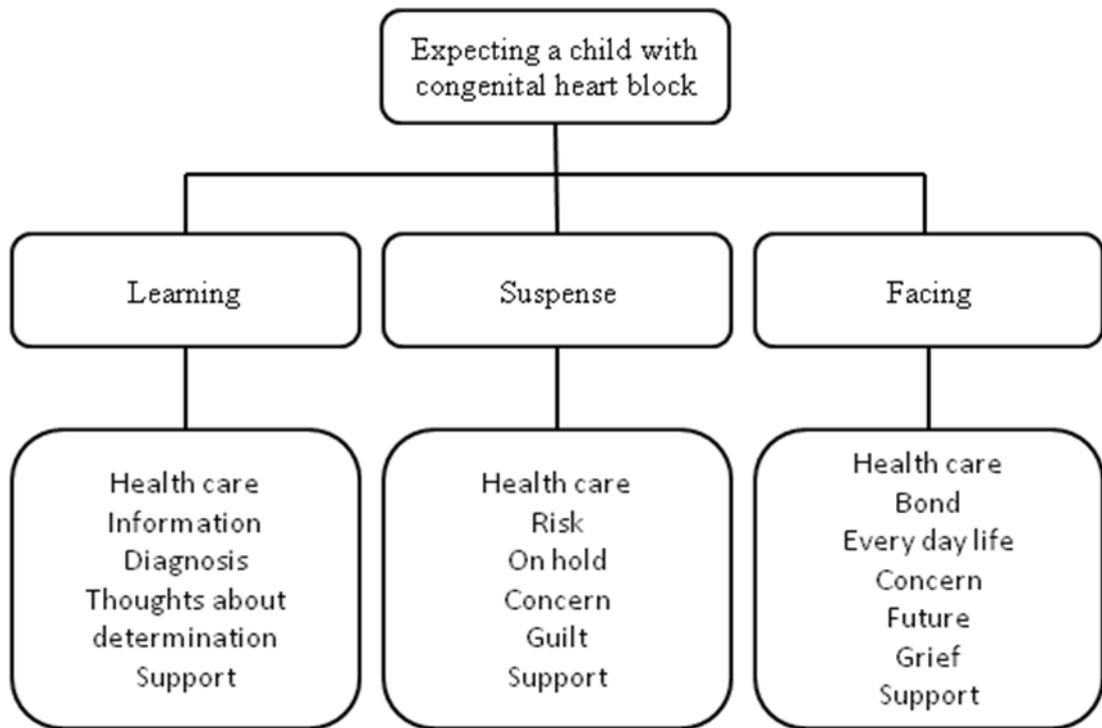


Figure 6. Description of theme, categories and codes from paper II.

4.1.2 Questionnaires, paper III, IV, V and VI

The questionnaires constructed in this thesis were based on the individual interviews described above. The questionnaires were used to prove or disprove the hypotheses formed from the results from the interviews and to retrieve answers to standardized questions from all Ro/SSA autoantibody positive women either participating in a surveillance programme or giving birth to a child with CHB identified in Sweden. The mothers were highly motivated to participate in the study and the response rate was 79% (79/100) in Doppler-group and 89% (78/88) in the CHB-group. When the response rate is above 70%, most resultant biases seem to disappear (Lydeard, 1991). Almost all women also chose to contribute with own comments or additional information that they wanted to share. Despite that the period of time since the pregnancy differed between the mothers, the answers were detailed and substantial. Even though the questionnaire itself was based on questions that emerged from the results of the interviews we might have neglected important aspects of the complex situation (Charlton, 2000). Since the questionnaire was only available in Swedish it is possible that women who had another native language did not feel confident in putting their thoughts into written text. It is also possible that some women did not understand the questions and therefore chose not to participate. The advantages of using a questionnaire are that data can be obtained in a structured

and systematic way and can be addressed to a large number of participants. This data collection method is relatively quick and not so costly (Charlton, 2000). Depending on the participant's experiences, interpretation of what a question mean may differ (Bork and Francis, 1985) and the method does not give the possibility for follow-up questions, like in the interview studies.

Table 2 summaries initial study aims, interview-derived hypotheses, questionnaire results and their implications.

Table 2. Summary of main questions investigated during the thesis.

Study question Explored	Interview-derived hypothesis	Questionnaire-deduced impact on hypothesis	Conclusion	Comment
Do Ro/SSA positive women know about the risk for CHB?	Ro/SSA positive women experience that they are not informed about the risk for CHB until they are pregnant, but prefer to know before pregnancy.	Ro/SSA positive women often experience that they are not informed about the risk for CHB until they are pregnant, but the majority reported they would have preferred to know before pregnancy.	Information on risk for CHB should be communicated when Ro/SSA positivity is detected.	Some individuals responded they preferred not to have knowledge about the risk before pregnancy. In total 6% of the Ro/SSA positive women stated knowing would have influenced the decision to become pregnant.
What do Ro/SSA positive women know about CHB?	Information provided is - insufficient - not understood - not readily available from public sources	The informant is important for whether the information is understood and experienced as sufficient. Information given by someone specialized in pediatric cardiology is significantly more often experienced as sufficient and understood.	Referral to a pediatric cardiology specialist can provide the mothers with better understanding of CHB. Correct and updated information on CHB needs to be more available for both health care personnel and patients.	More anxiety was experienced by mothers who felt they were not well informed or did not understand the information they got.
Not specifically addressed by structured interview questions	Mothers may learn about their Ro/SSA autoantibodies and their own rheumatic diagnosis or risk to develop rheumatic disease only when CHB is manifest in the child. The mother may postpone dealing with her own diagnosis/risk for rheumatic disease.	Questions not designed to address hypothesis Questions not designed to address hypothesis		A medical follow-up for the mother could be planned to ensure early treatment of developing rheumatic disease.
Do serial Doppler examinations during pregnancy induce undue anxiety in Ro/SSA positive women?	Serial Doppler examinations are experienced as a benefit and much support is given by the involved health care personnel.	The net impact of the serial Doppler examinations is positive, with support, guidance and information as examples of experienced benefits.	There is no reason to refrain from serial Doppler examinations due to fear of inducing undue anxiety in Ro/SSA positive women.	

How do the women experience Ro/SSA positive pregnancy and CHB emotionally?	Anxiety and worry for the fetal survival presents when the fetus has developed CHB. Support is given by family, friends and health care personnel. Professional psychological support is not offered.	Anxiety and worry for the fetal survival is common when the fetus has developed CHB. Support is given by family, friends and health care personnel. Most women in the CHB group however expressed need for additional support. Professional psychological support is seldom offered.	Offering professional psychological support should be considered when CHB has developed, as substantially fewer than would have accepted had been offered professional psychological support.	
How do the Ro/SSA positive women experience collaboration between the many involved clinics during their pregnancy?	To be supervised by many clinics constitutes a logistic problem to Ro/SSA positive women, and responsibility to carry information between clinics rests with the patient.	The interview-based hypothesis was not confirmed - when a larger group was consulted the majority felt collaboration between caregivers worked well.	Ro/SSA positive women reported that the current structure of support was satisfactory.	Notably approximately half of the women did not know who had the medical responsibility for themselves or for their child.
How do Ro/SSA positive women experience the postnatal period?	Mother's of a child with CHB are discharged from the hospital without sufficient information on the child's condition or what to do and whom to contact when medical complications occur.	Women giving birth to a child with CHB felt their own needs for care were not sufficiently met. Mothers of a child with CHB are often discharged from the hospital without sufficient information on the child's condition or what to do and whom to contact when medical complications occur.	Maternal needs for medical care and psychological support should be considered and met if possible. Structured follow-up should be planned when discharging a child with CHB from the hospital. Parents should be given oral and written information on whom to contact in case of medical need.	
Is there an increased risk for impaired neurodevelopment in children with CHB?			Both CHB and maternal SLE increase the risk for neurodevelopmental impairment.	Follow-up of children with CHB, especially if the mother has SLE should be planned to ensure that the child receives support needed if neurodevelopment is impaired.

4.1.3 Medical records, paper VI

To initiate this study we used the Swedish population-based cohort of individuals born with CHB and their siblings born to anti-Ro/SSA positive mothers during 1974-2009. Clinical data was collected for 114 individuals, 60 children with CHB and 54 of their siblings without CHB. In addition to medical records information about maternal diagnose and treatment during pregnancy were extracted from questionnaires, mentioned above.

4.2 INFORMATION

Information can be given and obtained in many different ways, depending on who is giving the information, who is receiving it and the interplay between those involved. Each situation when information is provided and attained is in some way unique. Below are descriptions of how the women in both the Doppler group and the CHB group received the information regarding the risk for CHB to develop in the fetal heart, who gave the information and how the mothers perceived the information. In addition, information was given on autoantibody positivity and/or disease in the woman herself.

4.2.1 Healthcare interactions

Women undergoing a high risk pregnancy commonly meet several different care givers during pregnancy. In the initial interview studies a nuanced appreciation of how the women experienced the situation with several care givers was expressed. Even though most women in paper I talked about the experience of good collaboration some women gave examples of problems and conflicts connected with meeting different care givers and expressed feelings of being responsible for being a communicator and coordinator between the different care givers. The women also reported that it was difficult to manage all different appointments and maintain presence at work. This illustrates the added emotional and practical load on women with a risk pregnancy like this. The lack of communication and coordination from the time from diagnosis to birth has also been described in a study with parents expecting a child with congenital diagnosis (Askelsdottir et al., 2008). In the studies conducted within this thesis, 47% of the women in the Doppler-group met at least four care givers (paper III) and 15% of the women in the CHB-group met four or more care givers (paper IV). It must be pointed

out that all women in the Doppler group knew about their autoantibody positivity before pregnancy and therefore their pregnancies were regarded as a risk pregnancy from start. In most cases the women in the CHB group did not know about their autoantibody positivity before pregnancy and therefore attended the regular antenatal care programme until some deviation was observed. The majority of the women in these studies considered that the collaboration between the care givers was good (99/125). However, only 55% vs. 50% mothers in the Doppler vs. CHB group could recall who had the medical responsibility for herself and 45% vs. 48% could recall who had the medical responsibility for the child.

4.2.1.1 *Timing of information*

When the mother's own diagnosis of rheumatic disease was unknown, we observed that it was most likely that the information about risk for CHB was presented to the woman when she was already pregnant (paper II and IV). However, this was also true for a substantial part of women with known rheumatic disease and identified Ro/SSA autoantibodies (paper III). To not learn about the risk until far into a pregnancy was described by some women like "being faced with an accomplished fact", and that they felt powerless. More than half of all women 54% (87/161), stated that they would preferred to have the information about the risk for CHB before pregnancy while 18% stated they would not have wanted to know and 28% did not know if they wanted to know before pregnancy. Whishes for adequate information when having to deal with parental decision-making in congenital heart diseases was also observed by Hoehn and colleagues (Hoehn et al., 2004). The answers show that it is important to share information available as soon as the autoantibody positivity is known. Information before or during initial stages of pregnancy may help the women and families to prepare and discuss the potential situation with health care professionals.

4.2.1.2 *The informant*

The person that informed the woman about a potential risk for heart block differed depending on when the autoantibody positivity was discovered. The content of the information on CHB also differed considerably depending on where the mother lived and who she met at the care unit as described below.

4.2.1.3 Initial informant

For 50% of the women from paper I and III the first person to inform the Ro/SSA positive women about the risk for CHB was the rheumatologist, usually before pregnancy in connection to information about the autoantibody positivity when it was discovered. Other persons to first give information on the risk CHB to women who later participated in the Doppler surveillance programme was an obstetrician (7%), a midwife (13%) or in 29% other persons (friends, family and in two cases a university teacher). For the women in the CHB-group a midwife at the antenatal clinic was often the first to discover that the fetal heartbeat frequency was lower than expected. At this stage the mothers usually received information only on that there was something amiss with the baby's heart frequency. This generally, but not always, depending on where the mother lived, led to a consultation with medical expertise where some, but often inadequate information on CHB was given. Considering the rarity of CHB, the low level of this specific knowledge, especially in peripheral units of the health care system is hardly surprising, and it can be difficult to accumulate adequate experience in unusual diagnosis to impart the information accurately (Crang-Svalenius et al., 2003; Larsson et al., 2010) During the last decades technical developments have brought many positive effects in diagnosing, resulting in detection and treatment of fetal malformations to a larger extent. This puts the health care personnel in a new situation, as they are expected to cope with the complexities of diagnosis and decisions, while at the same time being sensitive to the feelings of the parents, to be aware of their own emotions, and to keep parents informed (Birkeland et al., 2011).

4.2.1.4 Major informant

For the women who attended a Doppler surveillance programme or women in the CHB-group who were referred to a pediatric cardiology center the major informant was the pediatric cardiologist. For the group that for different reasons did not meet a pediatric cardiologist, the major informant was often a rheumatologist or an obstetrician.

4.2.1.5 Information content

Depending on where the woman lived and who she met in the chain of care the content of the information differed a lot.

4.2.1.5.1 Information on risk for CHB (paper I and III)

Almost all women who knew about their autoantibody positivity before pregnancy got information that a future pregnancy could involve additional risks and rather focused on the need for attending specialist antenatal care during pregnancy than on any expected risk for the fetus. However, the information was most often given to them when they were already pregnant and the vast majority (99%) of the women in the Doppler-group felt they understood the information about the risk of CHB in the expected infant. Although the majority had received the information after becoming pregnant, notably, most of the women reported that they would have preferred to be informed before the pregnancy.

4.2.1.5.2 Information on CHB (paper II and IV)

Most of the women in the group that gave birth to an infant with CHB got the information about CHB when they were already pregnant. They expressed a feeling of being faced with an accomplished fact, and described the situation as overwhelming and disconcerting. It was clear that the information and procedures differed a lot depending on where in Sweden the family lived and whom they met in the health care system. Being in a stressed situation gave them less time to adjust to and plan and prepare for the situation, and the health care personnel showed a lack of practice when trying to manage the situation and to give adequate information. All women wanted as much information as possible, even though it was sometimes hard to take in and understand what the situation would involve. This result is in line with other studies on how parents knowing that their child will be born with a congenital malformation answer (Fioravanti, 2002; Hoehn et al., 2004). Within the CHB-group only 41% of the women thought that the information was sufficient and 71% stated that they understood the information. The mothers who were informed by a pediatrician specialized in cardiology and who had the experience of how to inform about and how to follow up the condition after pregnancy, significantly more often thought the information was sufficient and comprehensible.

4.2.1.5.3 Information on maternal health - "I will deal with my situation later"

Almost all of mothers who came to the pediatric center for surveillance of the development of the fetal heart, had a rheumatic diagnosis and all were informed that

they were positive to Ro/SSA autoantibodies. If they had a rheumatic diagnosis, they had had the possibility to discuss their diagnosis with a rheumatologist at some point. For the participants in paper II and IV the situation differed considerably. The first sign of being at risk for a rheumatic disease in the future was the low heart rate in the fetus. The majority (76%) of the mothers in paper II, had no knowledge of their own autoantibody positivity. For women who learned about a rheumatic diagnosis or future risk for developing a rheumatic disease during their pregnancy, it was noticeable that information about their own health and the ability to adapt and manage this new situation was secondary. It was not uncommon that they said that they did not have time to think about their own condition yet, or that no one had informed them in a sufficient way. Some expressed that it was hard to get a perspective and understand the prognosis. The most common approach was to concentrate on the infant's condition and to postpone thoughts and reactions on their own condition. For some of the women in paper II the interview situation was the first time that they actually talked about and actively thought about their own autoantibody positivity and its implications.

4.2.1.5.4 Missing information

When interviewing the women (paper I, II), they expressed that information was missing in different ways. Women attending the Doppler/Ultrasound surveillance programme, expressed that the information from the pediatric cardiologist was sufficient. It was however hard to find information elsewhere, either to find out more or verify the information given to them. Again, for women who got information about that their child had CHB during pregnancy the situation was different. They expressed that the staff had sparse information to give. The information was not sufficient and the lack of experience among health care personnel was obvious in many situations. The results from the questionnaires (paper III, IV) showed a slightly different picture compared to the interview studies; in the Doppler-group 14% felt that the information on CHB was not sufficient and in the CHB-group 59% thought the information was not sufficient.

The knowledge about the connection between Ro/SSA autoantibodies and CHB has grown considerable over the last ten years (Salomonsson et al., 2002) and so has also the possibility to detect early signs of heart block (Sonesson et al., 2004). Since CHB is a rare condition it is not likely for a caregiver to encounter this situation frequently, and the information available is brief. Structured surveillance programmes and adequate information is not yet accessible in all parts of the country. Information

on rare diseases signify a special problem for which fully updated information cannot be expected at all remote units, and the need for policy's and plans for rare diseases have been highlighted lately (Forman et al., 2012).

4.2.1.5.5 Comprehending information

The language is the key to much of our communication; it gives us words to express experiences, feelings and to share information. When analyzing whether the women had the knowledge about the connection between autoantibody and the risk for the fetus to develop CHB, we found that the Doppler-group reported a high grade of understanding this connection (92%). Analyzing the same question for the CHB-group the reported understanding of the connection was lower (64%). Notably, the majority in the Doppler-group got the information about the connection from a practiced pediatric cardiologist at a highly specialized center in a structured manner. The demographic parameters of the CHB-group differed considerably and the majority of the women got the information from someone that not was specialized, the information was given in a peripheral unit, and also the information was given in a more acute way when the first signs of heart block were observed.

It is shown that families filter prenatal diagnostic information through their own personal and cultural frameworks and that this may help them to process it into a context that has a meaning for them. However, most families do not have previous understanding of genetic or fetal development and are therefore unprepared for the scope of medical information they will have to process, and can have difficulties in believing what they are told (Allen and Mulhauser, 1995; Maijala et al., 2002). When we asked the women in both groups, whether the information about the risk for heart block would have influenced their decision on having a child or not, 79% in the Doppler group and 57% in the CHB group denied. However, it must be emphasized that the question is asked retrospectively and it is in a way a hypothetical standpoint.

In both the Doppler group and the CHB group the educational level was high. The majority had two or more than two years of university education, 72% and 53% respectively. This indicates that the women were used to grasp information and are probably used to find and acquire adequate information by themselves.

4.2.2 Self-sought information

All women in these studies tried to seek for information on their own in some way, even if they thought that the information given to them was accurate and understandable. This is also described by others and the need of additional information after receiving information about suspected malformation or risks is great according to a study by Maijala and colleagues 2002 (Maijala et al., 2002). Also, parents often seek information independently about their unborn child's condition from available literature and internet (Askelsdottir et al., 2008).

4.2.2.1 *Alternative sources*

Different sources to seek information were used by almost all women as reported in both interview and questionnaire studies (papers I-V). During the last two decades Internet has grown to be a main source of information for the general public (Chauhan et al., 2012), also regarding health issues and it was used by many mothers in our study (data not shown). Other sources were books, and also to seek information from family, friends and teachers.

4.2.2.2 *Content and quality*

Even though the women did find alternative sources to get information, the content and quality differed a lot and was not updated. Information both in the literature and from the Internet was inadequate and diminutive in many cases. Accurate information was very hard to find for some of the women (paper I). In addition, the condition is very rare, and the knowledge about the connection between Ro/SSA autoantibodies and risks for the fetus during pregnancy as well as surveillance and treatment options is scarce.

4.2.3 Information - Summary

The information available on heart block is limited both for health care personnel as well as in the society as a whole. It can be assumed that it is unlikely that involved personnel in the chain of care surrounding a pregnant woman will come across this condition often enough to manage the situation without close collaboration with colleagues. We found that the information on heart block given differed a lot depending on where the woman lived and who she met in the chain of care. This thesis shows that there is a large difference in how the women understand the information

depending on if it is communicated to her from a pediatric cardiologist with the experience of the condition and handling of the situation, compared to someone not specialized in pediatric cardiology. In a study focusing on parents' need of information when their child were at risk to be born pre-term 78% agreed that the consultation relieved some of their worry and anxiety about their child when being informed by an antenatal specialist (Yee and Sauve, 2007). Our data show that the majority of the involved women wanted the information about risks connected to their autoantibody positivity as soon as it was detected, if possible before pregnancy, to be able to adjust to and prepare for the situation. The women who got information about their autoantibody positivity at the same time as their child was diagnosed with CHB did not get the opportunity to discuss their situation in a more controlled setting. When trying to find information on their own, the women had difficulties to find information that was reliable and updated.

Increased awareness and knowledge of CHB is needed, and adequate information about the risk of CHB should be given to the woman as soon as Ro/SSA autoantibodies are detected. To get updated and adequate information the women should be given information from someone who is experienced in the field and the information should preferably be given both verbally and in written form (Asplin et al., 2012). Ideally, information online should also be provided, to be easily accessible both for involved health care personnel and for the families. To be connected with or referred to a specialized center during pregnancy benefits the women.

4.3 EMOTIONAL RESPONSE IN RO/SSA POSITIVE PREGNANCIES

Information on CHB led to some kind of emotional reaction for all women in this study, and their reactions among other things depended on when, where and how and from whom the information came. Often the information led to a feeling of being in a stressful situation and the women expressed a feeling of being subjected to an unyielding fact, and described the situation as overwhelming and disconcerting.

4.3.1 Feeling safe or not, in an uncertain situation

Results from the studies included in this thesis show that the feeling of being secure was mainly based upon whom the women met in the chain of care and the quality of the information given to them. For the women in the Doppler group the uncertain situation occurred during GW 18-24 when there is a risk for the fetus to

develop CHB. All these women were referred to a pediatric cardiologist center for the purpose to detect early signs of AV-block by using Doppler/Ultrasound technique. The overall responses from these women were that they felt safe with the supervision and the interaction with the staff at the specialized clinic. They felt welcomed to the cardiology center, well cared for and well informed by the staff involved. In the Doppler group, 61% of the women stated that the extra examinations influenced their pregnancy, but almost all commented that the influence was positive and that the situation had advantages. The women made clear that the Doppler examinations in a way were a positive factor giving them a stronger connection and a possibility to interact with their unborn infant. In some cases they also felt it was an improvement in the relationship with their partner during this uncertain situation. This was also found in a study by Kovalchin and colleague when looking at impact of fetal echocardiography (Kovalchin and Silverman, 2004). Some women also described that it was a relief that someone shared the responsibility and guided them through the risk period (paper I). It is notable that 66% of all women responding to the questionnaire (paper III) felt calm before the Doppler examinations despite the complex situation. This highlights the need for specialized care with experienced personnel with practice of communicating and managing complex and traumatic situations (Birkeland et al., 2011; Zecca et al., 2006).

For women in the CHB group, the situation was very different compared to the Doppler group. They got the information without being prepared, often during a regular examination at the antenatal clinic. The lack of experience among the involved personnel appeared to strengthen a feeling of being insecure (paper II and IV). When a fetal abnormality is detected, information on prognosis is often variable and uncertain (Howard, 2006). The women in the CHB group in most cases also had to handle two diagnoses at the same time. The majority (76%) of the women in paper II were without symptoms of a rheumatic disease when the heart block was detected in the fetus, and in most cases did not know about their autoantibody positivity. These findings correlate to similar previous findings that Ro/SSA-positive mothers are often without signs of rheumatic disease and the Ro/SSA positivity unknown at the time of CHB development in the fetus (Julkunen and Eronen, 2001; Press et al., 1996). As described earlier, the woman's own potential diagnose or risk for development of rheumatic disease was not always discussed, and it was very common for the woman to postpone the insight of what it could mean.

4.3.2 Feelings of concern and anxiety

High levels of anxiety and psychological distress have been documented in pregnant women when a fetal malformation is suspected, diagnosed (Petersen and Jahn, 2008) or when the diagnosis appears ambiguous (Kaasen et al., 2010). The women in the CHB group were significantly more stressed and felt more anxiety when thinking about their child than the women in the Doppler group ($p=0.0003$). The difference is probably based on the fact that the women in the CHB group actually got the information about their child's heart block and the consequences connected with the grave and potentially lethal condition whereas the women in the Doppler group during GW 18-24 got the information that their child, for the time being, not had developed CHB. For one third of the women in the Doppler group the period between GW 18-24, just before visiting the pediatric cardiologist for the purpose of detecting a potential fetal heart abnormality, was the time when they were most anxious. In the CHB group about three-fourths of the women dread what could happen to their child during pregnancy. The feeling has been described as "knowing but not knowing" (Askelsdottir et al., 2008; Sandelowski and Jones, 1996) with extra stress and tension throughout the pregnancy. In general, women undergoing a high-risk pregnancy will experience more negative emotions related to their pregnancy than women with uncomplicated pregnancies (Gupton et al., 2001). Many women with high-risk factors for fetal malformation show high levels of anxiety immediately before the ultrasound scanning, but after the examination the levels decrease and continue to decrease longitudinally over a period of follow up (Brisch et al., 2003). The main emotional characteristics of high-risk pregnant women include anxiety and uncertainty (Clauson, 1996). As mentioned above the opportunity to have a consultation with an antenatal specialist (Yee and Sauve, 2007) may relieve some worry and anxiety, which we also observed in our studies where getting adequate information from a pediatric cardiologist made the women significantly more secure when leaving the hospital ($p=0.008$) and during the first weeks at home ($p=0.02$).

4.3.3 Suspense and "on hold"

When having the knowledge that the fetus was at risk to develop CHB or that the fetus had developed CHB it was common to describe the situation as being kept in suspense and putting the pregnancy "on hold". This has also been reported in a study describing what women feel while they are waiting for the results after invasive testing

(Carolan and Hodnett, 2009). When the fetus is at risk during pregnancy it has also been described as “having one foot in - one foot out”, meaning that the women feel that they could not emotionally totally invest in the pregnancy (Cote-Arsenault and Marshall, 2000). In a study by O`Brian and colleagues women described the situation as “putting the pregnancy in the back of their mind” and trying not to focus on the pregnancy, and not prepare anything for their child during pregnancy (O'Brien et al., 2010). In our study the results showed that it was significantly harder to enjoy pregnancy and to plan for things they wanted to do together with the child for the women in the CHB group compared to the Doppler group. However, the women interviewed in both groups described that it was hard to acknowledge the pregnancy and to attach to the unborn infant during pregnancy (paper I, II). A potential effect of the management strategy of putting the pregnancy on hold is potentially less time for preparing for parenthood. Women who gave birth to an infant with CHB reported feelings of uncertainty and hesitation when approaching their infant after it was born (paper II, IV).

4.3.4 Feelings of guilt

Results from paper II and IV show that 48% of the women who expected and gave birth to a child with congenital heart block expressed that they felt guilt and that it was their fault that the child had developed CHB. When a woman becomes pregnant, the mental and psychological preparation for parenthood may start a long time before the pregnancy is a fact, but increases during pregnancy (Condon, 1997; Hjelmstedt et al., 2006; Leifer, 1977). As described, fantasies about the child and what life will be like as a family, as well as increased emotional sense have been suggested to contribute to the preparation for parenthood (Stern and Bruschiweiler-Stern, 1998). When it is a fact that the fetus has an abnormality, parental expectations dash (Larsson et al., 2010), and they have to give up the picture they envisioned. Often feelings of guilt is present, and also grief, sadness and feelings of having lost the fantasized perfect infant, and the fear that one had a role in causing the defect (Brosig et al., 2007; Fioravanti, 2002; Howard, 2006). In CHB, the association with maternal autoantibodies is strong, and Ro/SSA autoantibodies have been demonstrated to directly induce AV-block in experimental models (Ambrosi et al., 2012). However, the recurrence risk being only 12-17% despite persisting autoantibody levels in the mother indicates that additional factors influence fetal outcome in response to autoantibody exposure. Recent studies in

both experimental models (Strandberg et al., 2010) and humans (Görge, 2013) indicate that fetal genes are a main factor determining whether CHB develops or not in response to Ro/SSA auto antibodies. This new knowledge demonstrates that genetic fortuitousness of common genetic alleles is a main factor of disease pathogenesis and may help in overcoming feelings of guilt. Interestingly, there is also a significant paternal increase in transmission of the susceptibility alleles (Görge, 2013).

4.3.5 Thoughts about determination

When realizing that congenital heart block had developed in the fetal heart an initial feeling of uncertainty and doubtfulness of continuing the pregnancy was sometimes present (paper II, IV). It is known that acute grief reactions are similar to the experiences following a stillbirth or neonatal death (Broen et al., 2004; Zeanah et al., 1994). This feeling was however temporary and passed for the vast majority when they had had a chance to adjust to the information and situation. For one couple, who had experienced losing a child due to CHB before, the decision of ending the pregnancy was made when signs of CHB occurred once again (paper II).

4.3.6 Emotional response - Summary

Getting information that something is wrong with the expected child is always overwhelming. It is of great importance to take each individual's situation into consideration when delivering bad news. To make the woman feel secure in the uncertain situation and provide time to ask questions is important. Thoughts about determination, at least as an initial reaction, and feelings of guilt are common, and this needs to be handled by professionals interacting with the families involved. Being at risk as well as knowing that the fetus had developed CHB made the women in many cases putting the pregnancy "on hold". Trying not to think about being pregnant, not planning for a child and not fully acknowledging the pregnancy for some time was common. Professional support and knowledge about this among the health care staff in the chain of care is important.

4.4 SUPPORT

4.4.1 Given support

Support given to the women in this study differed a lot depending on where the woman lived and whom she met. The vast majority of participating women had

received good support from their own family and friends (paper III and IV). Depending on whether the woman was at risk for having a child with CHB or actually got a child with CHB (Doppler vs. CHB group) the experience of sufficient support differed a lot. In the Doppler group 95% of the women felt that the support was enough, compared with the CHB group where only 64% of the women were satisfied with the support given to them ($p=0.0001$).

4.4.1.1 *Supporters*

In the Doppler group 65% of the women had four or more people supporting them (both non-professionals and professionals) and the corresponding proportion for the CHB group was 51%. One of the reasons why the women in the Doppler group reported that they had more supporting people around them could be that they participated in the surveillance programme. Women in the CHB group reported support from parents in law and friends less often than women in the Doppler group (paper V).

4.4.1.2 *Support need fulfillment*

The women who participated in the Doppler surveillance programme were generally satisfied with the support they had received during pregnancy, both from professional care givers and from significant others. The contacts seemed to encompass different needs, but both kinds of contacts were described as crucial for their sense of wellbeing. The women who had support from their family and friends e.g. a wider social network, and knew who to contact in the health care system felt less alone and more secure (paper V). The experience of the collaboration between the involved care units were perceived as good by 81% of the women. However, it was not always clear for the mothers who had the medical responsibility for them or for the child (Table 2 in paper III). Women in the CHB group reported a greater need for more support (53%) than what they actually got. It must be highlighted that this group in general did not get support from a specialized pediatric cardiologist. Also the women in the CHB group felt that the collaboration between care units was acceptable but there was an uncertainty, as in the Doppler group, about whom had the medical responsibility for the women herself (50%) and for the child (57%). In paper II some women reported a delay after being referred from the midwife who had observed the initially abnormality in the fetal heart beat frequency, to the time of the correct management due to lack of experience from the physician. An abnormal finding often comes unexpectedly a may

be shocking for the women. It is therefore important to give information about the finding to the women without time-lag and in a suitable environment (Larsson et al., 2010). As mentioned earlier in this thesis, CHB is a very rare and uncommon condition and it is not likely to accumulate knowledge at all remote care units.

4.4.2 Desired support

The overall finding in this study is that women at risk for having a child with CHB or women who actually got a child with CHB got the best professional support from a specialized pediatric cardiologist. This finding correlates well with a study by Montis et al where women reported a very high level of satisfaction of the support given from the staff at a pediatric cardiology unit (Montis et al., 2010). The positive effects of fetal echocardiography have also been discussed in a study by Björkhem et al. where fetal echocardiography was indicated to be very important to families who previously had a child with malformations (Björkhem et al., 1997). In their studies of fetal echocardiography and psychological effects Sklansky and colleagues found that a vast majority had chosen to undergo fetal echocardiography in subsequent pregnancies (Sklansky et al., 2002). In our studies, women who not had the opportunity to receive support from a specialized pediatric cardiologist reported a lack of knowledge among medical professionals about how to handle the pregnancy and how to manage the situation. In a study by Hunfeld et al. the women were significantly more positive to the prenatal consultation when meeting a physician with expertise knowledge in the area, especially shortly after hearing the bad news (Hunfeld et al., 1999).

4.4.2.1 Additional professional support

Decades of research demonstrates that women's psychosocial health strongly influences the child (Rosenberg et al., 2010). Paper I, II of this thesis and other research projects demonstrate an increased anxiety in women in connection to fetal echocardiography (Rosenberg et al., 2010; Sklansky et al., 2002). However, women report that the advantages of having fetal echocardiography outweigh the disadvantages (Sklansky et al., 2002). It is of importance to pay attention to the women's psychological well being during the period of undergoing Doppler/ultrasound examination during GW 18-24 to detect early signs of CHB, and to offer counseling throughout the pregnancy. In the CHB group only 21% of the women were offered psychological support, even though 38% of the mothers had accepted psychological

support and 44% did not know. Based on the results from paper I and the results from the questionnaire-study, paper IV, and from a study by Brosig et al., it should be considered to offer women extra professional support when a fetal malfunction has been detected (Brosig et al., 2007).

4.4.3 Support - Summary

Women undergoing risk pregnancies such as Ro/SSA-related pregnancies need support from family and friends. When the condition is rare like CHB, adequate care and support from medical staff with experience of managing complex situations is important. Offering consistent support throughout the pregnancy and ensure collaboration between the involved care units will influence the pregnancy in a positive way. Despite the stress and tension connected with Doppler/ultrasound examinations, it was a clear benefit for all women to attend the surveillance programme and they reported that the interaction with the staff at the pediatric cardiology clinic made them feel secure. However offering extra psychological support should be considered important especially for those whose child is diagnosed with CHB.

4.5 ORGANIZATION OF CARE AROUND RO/SSA POSITIVE PREGNANCIES

4.5.1 Primary care and specialized centers

In sparsely populated districts the hospitals generally do not have specialists in all medical fields. This can lead to that a physician's practicing in such a setting lack practice and knowledge about the needs for Ro/SSA positive women and their fetus during pregnancy which can cause a delay in treatment, surveillance and support. Hospitals in the major cities provide closer access to tertiary referral clinics and specialists. Information on rare diseases, like CHB, signifies a special problem for which fully updated information cannot be expected at all primary care units, and the need for policy's and plans for rare diseases have been highlighted as previously mentioned (Forman et al., 2012).

4.5.2 Involved clinics and their coordination

When a woman is pregnant and in a high risk situation it is important that care givers collaborate and coordinate their care. Women who participated in the studies in this thesis reported that they had contact with several care givers in various

clinics such as maternity clinic, specialist maternity clinic, rheumatology clinic, pediatric cardiology and others. To be in a care situation with several stakeholders involved may induce a complex multifaceted situation for the mother-to-be. In paper I, women stated that they felt like they had to have the overall view over the pregnancy and act like a messenger between the different care-units they attended. However, as mentioned earlier, women from both groups in general reported satisfaction with the collaboration between the different care givers. Although the opinion of good collaboration dominated, only about half of the women could point out who had the medical responsibility for herself or for the fetus. This highlights the importance of clear communication and coordination about who is medically responsible for the women and their fetus.

4.5.3 Doppler examinations

When being Ro/SSA positive the risk for the fetus to develop CHB occurs between GW 18-24. To detect early signs of heart block and if possible treat the condition, women in paper I and III were referred from either their rheumatologist or the antenatal care to a Doppler/ultrasound surveillance programme at a pediatric cardiology clinic. The examinations were carried out during GW 18-24, usually once a week, but the time span between the examinations and the choice of action depended on the results from each examination.

4.5.4 Organization - Summary

Results from this work show that different professionals including specialists, family doctors and midwives can work together to complement each other and provide consistent information. However, referral to a pediatric cardiology clinic for examinations and consultation is important since CHB is a rare condition and mothers attending such a center reported significantly more often that they had understood the information and felt more secure and were less anxious after returning back home with their baby. Also, the period of time for possible treatment is limited between GW 18-24 and rapid detection and subsequent treatment is facilitated at a highly specialized center.

4.6 LOSING THE CHILD IN UTERO OR IN CONNECTION WITH BIRTH

As described in section 1.7.2, CHB is a condition with high mortality.

During the work with this thesis, mothers that lost their child late in pregnancy or in connection to birth were among the interviewed (paper II). For two of these mothers, the interview situation was the first time that they had the possibility to share their experiences and thoughts. The mothers that lost their child all described that they had the opportunity to see and hold their baby if they wanted to and they could introduce the baby to siblings and family. The mothers also described that they had the chance to collect a few memories if that was their wish. However, all women described that the lack of experience of CHB from the staff did complicate the situation. Losing a child during pregnancy or in connection to birth is an inconceivable and extremely stressful type of loss and the dimensions of parental grief are diverse, (Cacciatore et al., 2008; Kavanaugh and Moro, 2006). The grief is profound and unique for each individual and the loss of a stillborn baby has been described as a complex loss (Geerinck-Vercammen, 1999; Hutti, 2005). There are assertions that both mothers and fathers bond with their unborn baby early in pregnancy (Klass et al., 1996). The stillborn baby is a part of the parent's identity in the form of hopes and fantasies that come with parenthood (Geerinck-Vercammen, 1999). Stillbirth usually occurs within a family context, where the mother and father, but also older siblings, and extended family members are affected (Avelin et al., 2011; Cacciatore et al., 2008; Estok and Lehman, 1983). It is important that the staff involved offer opportunities for the parents to see and hold their baby (Erlandsson et al., 2013). Some stillborn babies have siblings who are waiting for a little sister or brother and in addition to the loss of the expected baby, siblings also lose their status as a big brother or a big sister (Avelin et al., 2011). Children's grief and their understanding of death are aligned to their intellectual development and involve a gradual process (Black, 2005; Dyregov and Dyregov, 1999). During the interviews this was highlighted by some mothers (paper II)

4.7 THE POSTNATAL PERIOD

4.7.1 At the hospital

The care after delivery was perceived differently between the Doppler and the CHB group. Although both groups were generally satisfied with the care of their newborn infant, the women in the CHB-group apprehended the care of them self as significantly less satisfying than the women in the Doppler group. It should be taken

into consideration that in many cases the women and the infants in the CHB group were separated directly after birth due to the infant's condition. Also, the women in the CHB group perceived the collaboration between the involved care units as less satisfying than the women in the Doppler group. Again this could be a consequence of the fact that the infants in the CHB group had to undergo immediate specialist care, and that the wards were rather far apart.

4.7.2 Coming home with a child with or without CHB

The women in the CHB group felt significantly less secure when coming home with their infant than the women in the Doppler group ($p=0.0012$) (paper V). There was also a significant correlation between feeling less secure and lack of understanding the information given ($p=0.0303$). The support given to women in the CHB group from family and friends was reported poorer compared to the Doppler group. The feeling of being afraid and anxious among the women in the CHB group after coming home from the hospital was significantly correlated to the given support from family and friends (paper V).

For families that lost their child there was often a lack of professional support to help to handle the grief and feeling of guilt. There was also insufficient support for going through the course of events and planning for a future pregnancy if that was what the couple wished for (paper II).

4.7.3 Child health care centers

Most women in both groups (Doppler and CHB) contacted the child health care center by themselves after coming home. Also in this part of the chain of care the experience and knowledge about CHB and the connection to Ro/SSA autoantibodies was in general sparse or missing and it was difficult to get information or support. Most women reported that they themselves had to inform the personnel at the care unit about the risk during pregnancy and the heart block.

4.7.4 Networking

In our study only 6% of the women in the CHB group had contact with another family with a child with CHB and almost one third had appreciated such a contact. Some women expressed that talking with someone that had been in a similar situation would have been helpful and others stated that they thought that it would have

been beneficial for their child to meet someone with CHB, especially when reaching adolescence. Among the women in the CHB-group nearly one third had participated in the information meetings organized by Karolinska Institutet regarding CHB. Lately the knowledge about the importance of networks and policies for rare diseases has increased (Aymé et al., 2008; Forman et al., 2012; Schieppati et al., 2008). By networking the capacity increases in patient groups and can empower individuals to act proactively in self-care strategies to improve health outcome and quality of life (Aymé et al., 2008).

4.7.5 Future perspective for the individual

When being Ro/SSA autoantibody positive each pregnancy is a risk pregnancy during GW 18-24 at a greater or lesser degree. On one hand, the woman herself may develop a rheumatic disease with time (Julkunen and Eronen, 2001; Rivera et al., 2009), and on the other hand if a child is born with CHB, the risk increases to 12-17% for the next sibling to be born with CHB. Getting adequate and sufficient information on the different aspects is of great importance when planning a future pregnancy, starting with information on the woman's autoantibody positivity as soon as it is known. It is also important to point out that the risk for heart block is low and that there are methods to supervise and if needed treat the condition.

4.7.6 Postnatal period - Summary

In both the Doppler and the CHB group the care of the child after delivery was in general perceived as satisfactory. However, when a child's health is at risk obviously stress for the mother/family increases. It was common that the infants and the mothers were separated for some time after delivery due to the infant's condition. It was also found that the women who gave birth to a child with CHB felt less satisfied with the care of themselves. Feelings of being forsaken were described. Throughout this work the lack of experience and knowledge about CHB and the connection to Ro/SSA autoantibodies among health care staff has been obvious, and we also found that the mothers who had a child with CHB felt significantly less secure when coming home from the hospital. Contact with another family with a CHB child was infrequent, but was desired by one third of the families. The need for adequate and sufficient information and support was clear, also when planning a future pregnancy if that was what the couple's wish.

4.8 OTHER FAMILY MEMBERS

This thesis is focused on the Ro/SSA autoantibody positive women and their experiences of pregnancy and the postnatal period. However, the family surrounding the woman must of course be taken in to consideration, including the partner as well as the siblings, if any, and extended family members. Future studies should be addressed to understand their situation. Information and support to the partner is of great importance to make it possible for him/her to process and understand the situation (Cacciatore et al., 2013). Also, we did not design studies aimed at investigating the experience of living with CHB, which would be helpful to better understand the support required by this rare group of individuals. One part of the thesis work was however deduced to a follow-up study of neuropsychiatric development in children with CHB and their siblings (below).

4.8.1 FOLLOW UP OF CHILDREN WITH CHB AND THEIR SIBLINGS (paper VI)

As described in the introduction, section 1.5, NLE can include many different manifestations and also neurologic such (section 1.5.3). Case reports of hydrocephalus, non-specific white-matter changes, calcification of the basal ganglia and vasculopathy have been published (Silverman and Jaeggi, 2010). Several studies have also been published on higher incidence of learning disabilities in children born to mothers with SLE compared to children born to mothers without SLE, especially if the child is male (Lahita, 1988; McAllister et al., 1997; Neri et al., 2004). When parents report signs of neurodevelopmental deviations in their children, a higher frequency of dyslexia and decreased mental and sequential mental processing have been shown (Askanase et al., 2010; Behan et al., 1985; Yoshikawa et al., 2010).

In paper VI we used the Swedish population-based cohort of siblings with and with and without CHB, including individuals born 1974-2009 to an anti-Ro/SSA positive mother in the study. The results from the study show that impaired neurodevelopment was reported in 16% (18/114) of all children during the follow-up time of 13.0 (8.2-17.5) years. The reported problems included speech (9%), motor (8%) and learning (8%) impairment, attention deficit (5%) and behavioral impairment (4%). It was significantly more common with attention deficient and learning deficient among children with CHB of mothers with SLE than among their siblings. To compare our

data with prevalence of impairment in neurodevelopment in the general population is difficult. One reason is the retrospective design of our study and another reason is that the described neurodevelopment problems are not strict medical or psychiatric diagnoses and therefore descriptions and definitions alter over time.

Five categories of problems were observed in this study and speech (9%), motor skill development (8%) and learning impairment (8%) were the most reported problems. In the general population speech impairment is reported to be between 1% to 15% in different studies (Law et al., 2000; Tomblin et al., 1997; Westerlund, 1994; Westerlund and Sundelin, 2000). Studies in clumsiness and motor skill development showed a prevalence of just above 6% (Kadesjö and Gillberg, 1998). Review articles on learning disabilities show a prevalence of around 5% (Lagae, 2008; Lyon, 1996). Contrary to the studies above, our study did not show any clear increased risk for impairment in neurodevelopment in children born to anti-Ro/SSA positive mothers compared to the general population. In our study, disturbances in motor skill development were more common in boys than in girls and also influenced by gestational age. Attention deficit were however significantly more common in children born to mothers with SLE and in children with CHB. An SLE diagnosis in the mother did also affect learning disabilities, and a trend towards learning disabilities being more common in children born with CHB was noted.

4.8.2 Follow up - Summary

With the results from paper VI in mind, information on a possible risk for impairment and follow-up of neurodevelopment should be considered for children with CHB, especially if the mother is diagnosed with SLE. Increased awareness among involved personnel in hospitals, child health care centers and schools as well as parents and careful management of these individuals and early diagnosis are ways to help these children to overcome their difficulties during childhood and school years and make sure that they obtain the support needed. To better understand the potential risk of neurodevelopment impairment in children exposed to Ro/SSA autoantibodies prospective case-control studies will however be needed.

5 CONCLUDING REMARKS

Congenital heart block may develop in the fetus during pregnancy in Ro/SSA positive women. CHB is rare, but a life threatening condition. The risk period for CHB to develop in the fetal heart is during GW 18-24. During this time, serial Doppler/ultrasound examinations may be used to detect early signs of CHB. If needed, treatment to prevent further progression or to even revert incomplete AV blocks, can then be given. In this thesis interviews and questionnaires were used to explore maternal experiences of Ro/SSA positive pregnancy with the aim to identify potential areas for improvement in care and routines.

A main finding of the studies was the experienced low awareness and knowledge of CHB and its association with Ro/SSA autoantibodies in the chain of care and in society as a whole. An apparent strong need to increase both availability and accuracy of information on Ro/SSA autoantibodies and CHB emerged.

Most women got the information on their Ro/SSA autoantibody positivity and the risk for development of CHB when they were already pregnant. However, the results imply that women prefer to be informed before entering pregnancy, which will help to plan for and adjust to the situation. When informing, it is however important to point out that the risk for CHB is low, and that there are possibilities to detect and if needed possibilities to treat the condition.

The serial Doppler/echocardiography examinations did not induce anxiety during pregnancy, which has been raised as an issue and criticism against performing such investigations in a group where the risk for a serious condition is still low. Instead, coming to a highly specialized center, being able to ask questions and get adequate information and guidance and interact with the health care personnel with experience and knowledge about Ro/SSA autoantibody positivity and the risks connected to that was experienced as a benefit by the women. When handling a pregnancy with a risk for a rare condition like CHB, highly specialized centers thus appears beneficial both from a medical and care related perspective. The knowledge of how to provide information, surveillance and if needed treatment and support must be kept updated. For some women extra psychological support appeared needed. Offering a follow-up call or an extra appointment after passing the risk period is one way to meet the need of some women. When a woman is pregnant with a child with CHB it is important to give correct and comprehensible information, and adjust to each individual situation.

An unexpected observation relating to health care organization and information was that the women giving birth to a child with CHB often were unsure of whom to contact in case of medical need after leaving the hospital. Clear information on where to turn to, both written and verbal, should be provided to the families and may be one way to decrease anxiety as a connection between not know where to turn for help and more anxiety in the mothers was observed. To bridge the gap between different care givers, information should also be provided to personnel at the child health care when a child with CHB is coming home. The mothers who gave birth to a child with CHB expressed a wish to get in contact with other persons with the experience of having CHB in their family. This could be offered through patient organizations or an internet-based forum.

The increased risk observed for neurodevelopmental impairment in children with CHB, especially if the mother has SLE, indicates that children with CHB would benefit from follow-up to identify neurodevelopmental impairments so they may get the support needed.

The mothers who received information on their own autoantibody positivity and their own rheumatic diagnosis or risk for developing a rheumatic disease at the same time as their child was diagnosed with CHB, tended not to deal with their own situation. Offering a medical follow up after delivery could benefit these women, and ensure support and appropriate medical care.

In summary, this thesis includes the first set of studies exploring maternal experience of Ro/SSA positive pregnancy. During this work, focus has been on performing a basic characterization of how the women perceived their situation during pregnancy. Future studies may explore the effects of interventions. This thesis could be used as a starting point.

6 ACKNOWLEDGEMENTS

This work was carried out at the unit for Experimental Rheumatology, Center for Molecular Medicine, Karolinska Institutet. During my time as a PhD student I have had the pleasure to meet and work with many interesting, skillful and helpful people. I would like to thank everyone who has contributed in one way or another to make this work possible. I would especially like to thank;

My main supervisor Marie Wahren-Herlenius: Being a member of your team has been a true joy! You are the best supervisor one can wish for! Thank you for your enthusiasm and your never ending confidence in me and in this project. For always being there to discuss all important things in life. To take this journey with you was fantastic and definitely worth waiting for!

My co-supervisor Elisabet Welin Henriksson: Without you, I never would have had the opportunity to do this! Thank you for introducing me to CMM.

My co-supervisor Sven-Erik Sonesson: Thank you for sharing your deep knowledge and great competence with me!

My co-supervisor Anna Hjelmstedt: For friendship for more than 15 years. We have shared so many things, including trips, dinner parties and sometimes a glass of wine...

The current and previous head of Rheumatology Unit: Ingrid Lundberg and Lars Klareskog, for making the rheumatology unit such a unique place, with excellent research opportunities for everyone.

The MWH research group: Susanna "Nånnis" Brauner For being so devoted to all science projects, also mine! *Vijole Ottosson* for taking care of everyone in the group and never forget a birthday. *Lasse Ottosson* for helping me with everything from my computer to trying to find things at 4: th floor and for always doing it with a smile! (Even though you belong to another group I consider you as a very important member in our group!). *Alex Espinosa*, welcome back, maybe your biggest adventure just started... *Marika Kvarnström*, for sharing your knowledge in clinical work as well as in life in general. And for all the apples! *Maria Sjöstrand*, a living proof of that beauty and science do go together, *Amina Ossoinak* for your nice personality, *Malin Hedlund* for being so enthusiastic and cool, *Jacob Brantberg* and *Lara Aqrawi*, for being so positive, *Sabrina Görgen* and *Amanda Skog* my fantastic friends, for among other things, making the trip to Istanbul totally unforgettable after experience the Hamam together as Susie Que, Peggy Sue and Barbara Ann.

Sabrina thank you for your lovely sense of humor and my lovely earrings! Good luck with your life adventure.

Amanda, my wonderful friend, what would this adventure have been like without you? Thank you for being there. For always listening and sharing. Your friendship is one of the best things this education brought along. You will always have a special place in my heart! One of these days when we do not only have to work, promise to teach me how to eat snails in that exquisite way you do...

All former members of the MWH group including; *Aurelie Ambrosi, Ariela Hoxha, Therese Östberg, Vilja Oke and Åse Elfving*. A special thanks to *Elisabeth Zeffer*, for your warm friendship and for all help with the questionnaire.

All doctors and nurses at the Pediatric Cardiology Unit at Astrid Lindgren for sharing your great knowledge, and always welcoming me to the clinic whenever I wanted. Especially thanks to *Håkan Eliasson, Anna-Karin Hammarstedt and Linda Langenfeldt*.

All co-authors and members of *The Swedish Congenital Heart Block Study Group!*

All present and former members of the Rheumatology and Neuroimmunology group.

A special thanks to the patient colleagues in the office at 5:th floor; *Jayjesh, Amanda, Inka, Jessica, Karine, Lina, Klementy, Therese and Ferdinand*

All former and present members of Vårdforskargruppen Reuma. Special thanks to *Susanne Pettersson, Malin Regarth and Li Alemo Munters*.

Research friends Anna Tjärnlund for being such a nice friend and always supportive! *Mia Fahle´n* and *Julia Romanowska* what would I have done without you?

Administration: Gunnel Bemerfeldt, Always so patient and nice, *Veronica Ebbesten Lindholm* and *Stina Nordman* for all help with administration tasks. Wonderful *Lillemor Melander*, Do you ever have a bad day?

My family: *Sven* my love, life companion and my very best friend! Thank you for always reminding me of what is most important in life, for surprising me, and of course, for such a great partnership in parenthood.

“It’s such a perfect day and I’m glad I spend it with you”

Our lovely children; *Agnes* and *Dag*, every day with you is an adventure and you bring me so much joy. I feel endless gratitude for being your mother, and I’m so happy that you decided to climb down from your tree to us...

My mother *Kersti* and sister *Malla* and *Kicken, Lena, Jesper, Jonas, Jacob, Tenta*, (for among other things, every Wednesday) and *Lisa* (darling “Kuss” always there when I need you!) for also being my family.

My parents in law Annie and Arne for always helping out, believing in me and making sure that we always have mandelmusslor.

My friends, all of you, thank you for being there!

Claes Gustavsson, thank you for helping me with the cover to the thesis.

And last but not least

I would like to thank all *women and families* that shared their experiences with me and participated in the studies. I have learnt so much from you. Without you this had never been possible!



7 REFERECES

- Ahman, A., Runestam, K. and Sarkadi, A., 2010. Did I really want to know this? Pregnant women's reaction to detection of a soft marker during ultrasound screening. *Patient Educ Couns*, 81(1): 87-93.
- Ainsworth, M.D., 1979. Infant--mother attachment. *Am Psychol*, 34(10): 932-7.
- Allen, J.S. and Mulhauser, L.C., 1995. Genetic counseling after abnormal prenatal diagnosis: facilitating coping in families who continue their pregnancies. *J Genet Couns*, 4(4): 251-65.
- Ambrosi, A. et al., 2012. Development of heart block in children of SSA/SSB-autoantibody-positive women is associated with maternal age and displays a season-of-birth pattern. *Ann Rheum Dis*, 71(3): 334-40.
- Ambrosi, A. and Wahren-Herlenius, M., 2012. Congenital heart block: evidence for a pathogenic role of maternal autoantibodies. *Arthritis Res Ther*, 14(2): 208.
- Andelfinger, G., Fouron, J.C., Sonesson, S.E. and Proulx, F., 2001. Reference values for time intervals between atrial and ventricular contractions of the fetal heart measured by two Doppler techniques. *Am J Cardiol*, 88(12): 1433-6, A8.
- Askanase, A.D., Izmirly, P.M., Katholi, M., Mumtaz, J. and Buyon, J.P., 2010. Frequency of neuro-psychiatric dysfunction in anti-SSA/SSB exposed children with and without neonatal lupus. *Lupus*, 19(3): 300-6.
- Askelsdottir, B., Conroy, S. and Rempel, G., 2008. From diagnosis to birth: parents' experience when expecting a child with congenital anomaly. *Adv Neonatal Care*, 8(6): 348-54.
- Asplin, N., Wessel, H., Marions, L. and Georgsson Öhhman, S., 2012. Pregnant women's experiences, needs, and preferences regarding information about malformations detected by ultrasound scan. *Sex Reprod Healthc*, 3(2): 73-8.
- Austin-Ward, E. et al., 1998. Neonatal lupus syndrome: a case with chondrodysplasia punctata and other unusual manifestations. *J Med Genet*, 35(8): 695-7.
- Avelin, P., Erlandsson, K., Hildingsson, I. and Radestad, I., 2011. Swedish parents' experiences of parenthood and the need for support to siblings when a baby is stillborn. *Birth*, 38(2): 150-8.
- Aymé, S., Kole, A. and Groft, S., 2008. Empowerment of patients: lessons from the rare diseases community. *Lancet*, 371(9629): 2048-51.
- Barclay, C.S., French, M.A., Ross, L.D. and Sokol, R.J., 1987. Successful pregnancy following steroid therapy and plasma exchange in a woman with anti-Ro (SS-A) antibodies. Case report. *Br J Obstet Gynaecol*, 94(4): 369-71.
- Behan, W.M., Behan, P.O. and Geschwind, N., 1985. Anti-Ro antibody in mothers of dyslexic children. *Dev Med Child Neurol*, 27(4): 538-40.
- Bergman, G., Eliasson, H., Bremme, K., Wahren-Herlenius, M. and Sonesson, S.E., 2009. Anti-Ro52/SSA antibody-exposed fetuses with prolonged atrioventricular time intervals show signs of decreased cardiac performance. *Ultrasound Obstet Gynecol*, 34(5): 543-9.
- Bergman, G., Jacobsson, L.A., Wahren-Herlenius, M. and Sonesson, S.E., 2006. Doppler echocardiographic and electrocardiographic atrioventricular time intervals in newborn infants: evaluation of techniques for surveillance of fetuses at risk for congenital heart block. *Ultrasound Obstet Gynecol*, 28(1): 57-62.
- Bierman, F.Z., Baxi, L., Jaffe, I. and Driscoll, J., 1988. Fetal hydrops and congenital complete heart block: response to maternal steroid therapy. *J Pediatr*, 112(4): 646-8.

- Birkeland, A.L., Dahlgren, L., Hägglöf, B. and Rydberg, A., 2011. Breaking bad news: an interview study of paediatric cardiologists. *Cardiol Young*, 21(3): 286-91.
- Björkhem, G., Jørgensen, C. and Hanséus, K., 1997. Parental reactions to fetal echocardiography. *J Matern Fetal Med*, 6(2): 87-92.
- Black, S., 2005. When children grieve. *Am Sch Board J*, 192(8): 28-30.
- Blanford, A.T. and Murphy, B.E., 1977. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. *Am J Obstet Gynecol*, 127(3): 264-7.
- Bork, C.E. and Francis, J.B., 1985. Developing effective questionnaires. *Phys Ther*, 65(6): 907-11.
- Boros, C.A., Spence, D., Blaser, S. and Silverman, E.D., 2007. Hydrocephalus and macrocephaly: new manifestations of neonatal lupus erythematosus. *Arthritis Rheum*, 57(2): 261-6.
- Brisch, K.H. et al., 2003. Coping styles of pregnant women after prenatal ultrasound screening for fetal malformation. *J Psychosom Res*, 55(2): 91-7.
- Britten, N., 1995. Qualitative interviews in medical research. *BMJ*, 311(6999): 251-3.
- Broen, A.N., Moum, T., Bødtker, A.S. and Ekeberg, O., 2004. Psychological impact on women of miscarriage versus induced abortion: a 2-year follow-up study. *Psychosom Med*, 66(2): 265-71.
- Brosig, C.L., Whitstone, B.N., Frommelt, M.A., Frisbee, S.J. and Leuthner, S.R., 2007. Psychological distress in parents of children with severe congenital heart disease: the impact of prenatal versus postnatal diagnosis. *J Perinatol*, 27(11): 687-92.
- Brucato, A. et al., 2001. Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. *Arthritis Rheum*, 44(8): 1832-5.
- Brucato, A. et al., 2003. Proposal for a new definition of congenital complete atrioventricular block. *Lupus*, 12(6): 427-35.
- Buyon, J. and Szer, I., 1986. Passively acquired autoimmunity and the maternal fetal dyad in systemic lupus erythematosus. *Springer Semin Immunopathol*, 9(2-3): 283-304.
- Buyon, J.P. and Clancy, R.M., 2003. Neonatal lupus syndromes. *Curr Opin Rheumatol*, 15(5): 535-41.
- Buyon, J.P. et al., 1998. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol*, 31(7): 1658-66.
- Buyon, J.P., Kim, M.Y., Copel, J.A. and Friedman, D.M., 2001. Anti-Ro/SSA antibodies and congenital heart block: necessary but not sufficient. *Arthritis Rheum*, 44(8): 1723-7.
- Buyon, J.P., Swersky, S.H., Fox, H.E., Bierman, F.Z. and Winchester, R.J., 1987. Intrauterine therapy for presumptive fetal myocarditis with acquired heart block due to systemic lupus erythematosus. Experience in a mother with a predominance of SS-B (La) antibodies. *Arthritis Rheum*, 30(1): 44-9.
- Buyon, J.P., Waltuck, J., Kleinman, C. and Copel, J., 1995. In utero identification and therapy of congenital heart block. *Lupus*, 4(2): 116-21.
- Buyon, J.P. et al., 1993. Identification of mothers at risk for congenital heart block and other neonatal lupus syndromes in their children. Comparison of enzyme-linked immunosorbent assay and immunoblot for measurement of anti-SS-A/Ro and anti-SS-B/La antibodies. *Arthritis Rheum*, 36(9): 1263-73.

- Byrne, M.M., 2001. Evaluating the findings of qualitative research. *AORN J*, 73(3): 703-6.
- Cabanas, F., Pellicer, A., Valverde, E., Morales, C. and Quero, J., 1996. Central nervous system vasculopathy in neonatal lupus erythematosus. *Pediatr Neurol*, 15(2): 124-6.
- Cacciatore, J., Erlandsson, K. and Rådestad, I., 2013. Fatherhood and suffering: A qualitative exploration of Swedish men's experiences of care after the death of a baby. *Int J Nurs Stud*, 50(5): 664-70.
- Cacciatore, J., Rådestad, I. and Frederik Froen, J., 2008. Effects of contact with stillborn babies on maternal anxiety and depression. *Birth*, 35(4): 313-20.
- Carolan, M., 2005. "Doing it properly": the experience of first mothering over 35 years. *Health Care Women Int*, 26(9): 764-87.
- Carolan, M. and Hodnett, E., 2009. Discovery of soft markers on fetal ultrasound: maternal implications. *Midwifery*, 25(6): 654-64.
- Charlton, R., 2000. Research: is an 'ideal' questionnaire possible? *Int J Clin Pract*, 54(6): 356-9.
- Chauhan, B., George, R. and Coffin, J., 2012. Social media and you: what every physician needs to know. *J Med Pract Manage*, 28(3): 206-9.
- Chen, X., Quinn, A.M. and Wolin, S.L., 2000. Ro ribonucleoproteins contribute to the resistance of *Deinococcus radiodurans* to ultraviolet irradiation. *Genes Dev*, 14(7): 777-82.
- Chen, X. et al., 2003. The Ro autoantigen binds misfolded U2 small nuclear RNAs and assists mammalian cell survival after UV irradiation. *Curr Biol*, 13(24): 2206-11.
- Chitayat, D. et al., 2008. Chondrodysplasia punctata associated with maternal autoimmune diseases: expanding the spectrum from systemic lupus erythematosus (SLE) to mixed connective tissue disease (MCTD) and scleroderma report of eight cases. *Am J Med Genet A*, 146A(23): 3038-53.
- Cimaz, R., Spence, D.L., Hornberger, L. and Silverman, E.D., 2003. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. *J Pediatr*, 142(6): 678-83.
- Clancy, R.M. and Buyon, J.P., 2004. Autoimmune-associated congenital heart block: dissecting the cascade from immunologic insult to relentless fibrosis. *Anat Rec A Discov Mol Cell Evol Biol*, 280(2): 1027-35.
- Clauson, M.I., 1996. Uncertainty and stress in women hospitalized with high-risk pregnancy. *Clin Nurs Res*, 5(3): 309-25.
- Condon, J., 1997. The correlates of antenatal attachment in pregnant women. *British Journal Med Psychol*, 70: 359-372.
- Cote-Arsenault, D. and Marshall, R., 2000. One foot in-one foot out: weathering the storm of pregnancy after perinatal loss. *Res Nurs Health*, 23(6): 473-85.
- Crang-Svalenius, E., Dykes, A.K. and Jorgensen, C., 2003. Maternal serum screening for Down syndrome--opinions on acceptance from Swedish women. *Scand J Caring Sci*, 17(1): 30-4.
- Crang-Svalenius, E., Dykes, A.K. and Jörgensen, C., 1996. Women's informed choice of prenatal diagnosis: early ultrasound examination-routine ultrasound examination-age-independent amniocentesis. *Fetal Diagn Ther*, 11(1): 20-5.
- Cuneo, B.F. et al., 2010. A management strategy for fetal immune-mediated atrioventricular block. *J Matern Fetal Neonatal Med*, 23(12): 1400-5.
- Dyregov, A. and Dyregov, K., 1999. Long-term impact of sudden infant death. *Death Stud*, 23(7): 635-661.

- Ekelin, M., Crang-Svalenius, E. and Dykes, A.K., 2004. A qualitative study of mothers' and fathers' experiences of routine ultrasound examination in Sweden. *Midwifery*, 20(4): 335-44.
- Elcioglu, N. and Hall, C.M., 1998. Maternal systemic lupus erythematosus and chondrodysplasia punctata in two sibs: phenocopy or coincidence? *J Med Genet*, 35(8): 690-4.
- Eliasson, H. et al., 2011. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. *Circulation*, 124(18): 1919-26.
- Elo, S. and Kyngäs, H., 2008. The qualitative content analysis process. *J Adv Nurs*, 62(1): 107-15.
- Erlandsson, K., Warland, J., Cacciatore, J. and Radestad, I., 2013. Seeing and holding a stillborn baby: mothers' feelings in relation to how their babies were presented to them after birth--findings from an online questionnaire. *Midwifery*, 29(3): 246-50.
- Eronen, M. et al., 2000. Short- and long-term outcome of children with congenital complete heart block diagnosed in utero or as a newborn. *Pediatrics*, 106(1 Pt 1): 86-91.
- Espinosa, A. et al., 2009. Loss of the lupus autoantigen Ro52/Trim21 induces tissue inflammation and systemic autoimmunity by dysregulating the IL-23-Th17 pathway. *J Exp Med*, 206(8): 1661-71.
- Espinosa, A. et al., 2006. The Sjogren's syndrome-associated autoantigen Ro52 is an E3 ligase that regulates proliferation and cell death. *J Immunol*, 176(10): 6277-85.
- Estok, P. and Lehman, A., 1983. Perinatal death: grief support for families. *Birth*, 10(1): 17-25.
- Eurenius, K., Axelsson, O., Gällstedt-Fransson, I. and Sjöden, P.O., 1997. Perception of information, expectations and experiences among women and their partners attending a second-trimester routine ultrasound scan. *Ultrasound Obstet Gynecol*, 9(2): 86-90.
- Figueiredo, B. and Costa, R., 2009. Mother's stress, mood and emotional involvement with the infant: 3 months before and 3 months after childbirth. *Arch Womens Ment Health*, 12(3): 143-53.
- Fioravanti, J., 2002. Issues related to prenatal diagnosis of congenital heart disease. *Neonatal Netw*, 21(6): 23-9.
- Forman, J. et al., 2012. The need for worldwide policy and action plans for rare diseases. *Acta Paediatr*, 101(8): 805-7.
- Franceschini, F. and Cavazzana, I., 2005. Anti-Ro/SSA and La/SSB antibodies. *Autoimmunity*, 38(1): 55-63.
- Friedman, D., Duncanson, L., Glickstein, J. and Buyon, J., 2003. A review of congenital heart block. *Images Paediatr Cardiol*, 5(3): 36-48.
- Friedman, D.M. et al., 2008. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. *Circulation*, 117(4): 485-93.
- Friedman, D.M. et al., 2010. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. *Arthritis Rheum*, 62(4): 1138-46.
- Friedman, D.M., Rupel, A., Glickstein, J. and Buyon, J.P., 2002. Congenital heart block in neonatal lupus: the pediatric cardiologist's perspective. *Indian J Pediatr*, 69(6): 517-22.
- Garcia, J. et al., 2002. Women's views of pregnancy ultrasound: a systematic review. *Birth*, 29(4): 225-50.

- Geerinck-Vercammen, C.R., 1999. With a positive feeling: the grief process after stillbirth in relation to the role of the professional caregivers. *Eur J Obstet Gynecol Reprod Biol*, 87(2): 119-21.
- Georgsson Ohman, S., Saltvedt, S., Grunewald, C. and Waldenström, U., 2004. Does fetal screening affect women's worries about the health of their baby? A randomized controlled trial of ultrasound screening for Down's syndrome versus routine ultrasound screening. *Acta Obstet Gynecol Scand*, 83(7): 634-40.
- Ginsberg, J.S. et al., 1992. Relationship of antiphospholipid antibodies to pregnancy loss in patients with systemic lupus erythematosus: a cross-sectional study. *Blood*, 80(4): 975-80.
- Glickstein, J.S., Buyon, J. and Friedman, D., 2000. Pulsed Doppler echocardiographic assessment of the fetal PR interval. *Am J Cardiol*, 86(2): 236-9.
- Graneheim, U.H. and Lundman, B., 2004. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today*, 24(2): 105-12.
- Gudex, C., Nielsen, B.L. and Madsen, M., 2006. Why women want prenatal ultrasound in normal pregnancy. *Ultrasound Obstet Gynecol*, 27(2): 145-50.
- Gupton, A., Heaman, M. and Cheung, L.W., 2001. Complicated and uncomplicated pregnancies: women's perception of risk. *J Obstet Gynecol Neonatal Nurs*, 30(2): 192-201.
- Görge, S., 2013. The HLA locus contains novel foetal susceptibility alleles for congenital heart block with significant paternal influence. *Annals of the Rheumatic Diseases*, 72: A56.
- Halcomb, E.J. et al., 2005. Nursing in Australian general practice: directions and perspectives. *Aust Health Rev*, 29(2): 156-66.
- Halcomb, E.J., Patterson, E. and Davidson, P.M., 2006. Evolution of practice nursing in Australia. *J Adv Nurs*, 55(3): 376-88; discussion 388-90.
- Handley, M. and Collins, A., 2008. Delicate threads: autoimmune complications in a high-risk pregnancy. *Nurs Womens Health*, 12(2): 139-45.
- Hershko, A., Heller, H., Elias, S. and Ciechanover, A., 1983. Components of ubiquitin-protein ligase system. Resolution, affinity purification, and role in protein breakdown. *J Biol Chem*, 258(13): 8206-14.
- Hjelmstedt, A., Widstrom, A.M. and Collins, A., 2006. Psychological correlates of prenatal attachment in women who conceived after in vitro fertilization and women who conceived naturally. *Birth*, 33(4): 303-10.
- Hoehn, K.S. et al., 2004. Parental decision-making in congenital heart disease. *Cardiol Young*, 14(3): 309-14.
- Honda, R., Ichiyama, T., Maeba, S., Sunagawa, S. and Furukawa, S., 2008. Male siblings with tibia-metacarpal type of chondrodysplasia punctata without maternal factors. *Brain Dev*, 30(4): 301-4.
- Howard, E.D., 2006. Family-centered care in the context of fetal abnormality. *J Perinat Neonatal Nurs*, 20(3): 237-42.
- Hunfeld, J.A. et al., 1999. Prenatal consultation after a fetal anomaly scan: videotaped exploration of physician's attitude and patient's satisfaction. *Prenat Diagn*, 19(11): 1043-7.
- Hussein, S.Z., Jacobsson, L.T., Lindquist, P.G. and Theander, E., 2011. Pregnancy and fetal outcome in women with primary Sjogren's syndrome compared with women in the general population: a nested case-control study. *Rheumatology (Oxford)*, 50(9): 1612-7.

- Hutter, D., Silverman, E.D. and Jaeggi, E.T., 2010. The benefits of transplacental treatment of isolated congenital complete heart block associated with maternal anti-Ro/SSA antibodies: a review. *Scand J Immunol*, 72(3): 235-41.
- Hutti, M.H., 2005. Social and professional support needs of families after perinatal loss. *J Obstet Gynecol Neonatal Nurs*, 34(5): 630-8.
- Izmirly, P.M. et al., 2011. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. *Circulation*, 124(18): 1927-35.
- Jaeggi, E.T., Hamilton, R.M., Silverman, E.D., Zamora, S.A. and Hornberger, L.K., 2002. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block. A single institution's experience of 30 years. *J Am Coll Cardiol*, 39(1): 130-7.
- Jaeggi, E.T. and Nii, M., 2005. Fetal brady- and tachyarrhythmias: new and accepted diagnostic and treatment methods. *Semin Fetal Neonatal Med*, 10(6): 504-14.
- Jonsson, R., Haga, H.J. and Gordon, T.P., 2000. Current concepts on diagnosis, autoantibodies and therapy in Sjögren's syndrome. *Scand J Rheumatol*, 29(6): 341-8.
- Julkunen, H. and Eronen, M., 2001. The rate of recurrence of isolated congenital heart block: a population-based study. *Arthritis Rheum*, 44(2): 487-8.
- Julkunen, H., Kaaja, R., Kurki, P., Palosuo, T. and Friman, C., 1995. Fetal outcome in women with primary Sjogren's syndrome. A retrospective case-control study. *Clin Exp Rheumatol*, 13(1): 65-71.
- Julkunen, H. et al., 1998. Immune-mediated congenital heart block (CHB): identifying and counseling patients at risk for having children with CHB. *Semin Arthritis Rheum*, 28(2): 97-106.
- Kaaja, R., Julkunen, H., Ammälä, P., Kurki, P. and Koskimies, S., 1993. Congenital heart block in one of the HLA identical twins. *Eur J Obstet Gynecol Reprod Biol*, 51(1): 78-80.
- Kaaja, R., Julkunen, H., Ammälä, P., Teppo, A.M. and Kurki, P., 1991. Congenital heart block: successful prophylactic treatment with intravenous gamma globulin and corticosteroid therapy. *Am J Obstet Gynecol*, 165(5 Pt 1): 1333-4.
- Kaasen, A. et al., 2010. Acute maternal social dysfunction, health perception and psychological distress after ultrasonographic detection of a fetal structural anomaly. *BJOG*, 117(9): 1127-38.
- Kadesjö, B. and Gillberg, C., 1998. Attention deficits and clumsiness in Swedish 7-year-old children. *Dev Med Child Neurol*, 40(12): 796-804.
- Kavanaugh, K. and Moro, T., 2006. Supporting parents after stillbirth or newborn death: There is much that nurses can do. *Am J Nurs*, 106(9): 74-9.
- Kaye, E.M., Butler, I.J. and Conley, S., 1987. Myelopathy in neonatal and infantile lupus erythematosus. *J Neurol Neurosurg Psychiatry*, 50(7): 923-6.
- Kelly, T.E., Alford, B.A. and Greer, K.M., 1999. Chondrodysplasia punctata stemming from maternal lupus erythematosus. *Am J Med Genet*, 83(5): 397-401.
- Klass, D., Silverman, P. and Nickman, S., 1996. *New Understanding of Grief. Continuing Bonds*. Taylor & Francis, London.
- Klippel, J.H., 1997. Systemic lupus erythematosus: demographics, prognosis, and outcome. *J Rheumatol Suppl*, 48: 67-71.
- Kowalcek, I. et al., 2003a. The influence of gestational age on depressive reactions, stress and anxiety of pregnant women and their partners in relation to prenatal diagnosis. *J Psychosom Obstet Gynaecol*, 24(4): 239-45.
- Kowalcek, I. et al., 2003b. Anxiety scores before and after prenatal testing for congenital anomalies. *Arch Gynecol Obstet*, 267(3): 126-9.

- Kovalchin, J.P. and Silverman, N.H., 2004. The impact of fetal echocardiography. *Pediatr Cardiol*, 25(3): 299-306.
- Kozlowski, K., Basel, D. and Beighton, P., 2004. Chondrodysplasia punctata in siblings and maternal lupus erythematosus. *Clin Genet*, 66(6): 545-9.
- Labbé, J.C., Hekimi, S. and Rokeach, L.A., 1999. The levels of the RoRNP-associated Y RNA are dependent upon the presence of ROP-1, the *Caenorhabditis elegans* Ro60 protein. *Genetics*, 151(1): 143-50.
- Lagae, L., 2008. Learning disabilities: definitions, epidemiology, diagnosis, and intervention strategies. *Pediatr Clin North Am*, 55(6): 1259-68, vii.
- Lahita, R.G., 1988. Systemic lupus erythematosus: learning disability in the male offspring of female patients and relationship to laterality. *Psychoneuroendocrinology*, 13(5): 385-96.
- Lalor, J.G. and Devane, D., 2007. Information, knowledge and expectations of the routine ultrasound scan. *Midwifery*, 23(1): 13-22.
- Larsen, T., Nguyen, T.H., Munk, M., Svendsen, L. and Teisner, L., 2000. Ultrasound screening in the 2nd trimester. The pregnant woman's background knowledge, expectations, experiences and acceptances. *Ultrasound Obstet Gynecol*, 15(5): 383-6.
- Larsson, A.K., Svalenius, E.C., Lundqvist, A. and Dykes, A.K., 2010. Parents' experiences of an abnormal ultrasound examination - vacillating between emotional confusion and sense of reality. *Reprod Health*, 7: 10.
- Law, J., Boyle, J., Harris, F., Harkness, A. and Nye, C., 2000. Prevalence and natural history of primary speech and language delay: findings from a systematic review of the literature. *Int J Lang Commun Disord*, 35(2): 165-88.
- Lee, L.A., 2009. The clinical spectrum of neonatal lupus. *Arch Dermatol Res*, 301(1): 107-10.
- Lee, L.A., 2010. Cutaneous lupus in infancy and childhood. *Lupus*, 19(9): 1112-7.
- Lee, L.A. and Weston, W.L., 1997. Cutaneous lupus erythematosus during the neonatal and childhood periods. *Lupus*, 6(2): 132-8.
- Leifer, M., 1977. Psychological changes accompanying pregnancy and motherhood. *Genet Psychol Monogr*, 95(1): 55-96.
- Litsey, S.E., Noonan, J.A., O'Connor, W.N., Cottrill, C.M. and Mitchell, B., 1985. Maternal connective tissue disease and congenital heart block. Demonstration of immunoglobulin in cardiac tissue. *N Engl J Med*, 312(2): 98-100.
- Llanos, C. et al., 2009. Recurrence rates of cardiac manifestations associated with neonatal lupus and maternal/fetal risk factors. *Arthritis Rheum*, 60(10): 3091-7.
- Lydeard, S., 1991. The questionnaire as a research tool. *Fam Pract*, 8(1): 84-91.
- Lyon, G.R., 1996. Learning disabilities. *Future Child*, 6(1): 54-76.
- Maijala, H., Astedt-Kurki, P. and Paavilainen, E., 2002. Interaction as an ethically sensitive subject of research. *Nurse Res*, 10(2): 20-37.
- Makino, S., Yonemoto, H., Itoh, S. and Takeda, S., 2007. Effect of steroid administration and plasmapheresis to prevent fetal congenital heart block in patients with systemic lupus erythematosus and/or Sjögren's syndrome. *Acta Obstet Gynecol Scand*, 86(9): 1145-6.
- Marsal, K. and Malcus, P., 2008. *Ultraljudsdiagnostik*. Studentlitteratur, Lund.
- Matthiesen, L. et al., 2005. Immunology of preeclampsia. *Chem Immunol Allergy*, 89: 49-61.
- McAllister, D.L. et al., 1997. The influence of systemic lupus erythematosus on fetal development: cognitive, behavioral, and health trends. *J Int Neuropsychol Soc*, 3(4): 370-6.

- McCain, G.C. and Deatrick, J.A., 1994. The experience of high-risk pregnancy. *J Obstet Gynecol Neonatal Nurs*, 23(5): 421-7.
- McNab, F.W., Rajsbaum, R., Stoye, J.P. and O'Garra, A., 2011. Tripartite-motif proteins and innate immune regulation. *Curr Opin Immunol*, 23(1): 46-56.
- Meleis, A.I., Sawyer, L.M., Im, E.O., Hilfinger Messias, D.K. and Schumacher, K., 2000. Experiencing transitions: an emerging middle-range theory. *ANS Adv Nurs Sci*, 23(1): 12-28.
- Mercer, R.T., 2004. Becoming a mother versus maternal role attainment. *J Nurs Scholarsh*, 36(3): 226-32.
- Michaelsson, M. and Engle, M.A., 1972. Congenital complete heart block: an international study of the natural history. *Cardiovasc Clin*, 4(3): 85-101.
- Mok, C.C. and Wong, R.W., 2001. Pregnancy in systemic lupus erythematosus. *Postgrad Med J*, 77(905): 157-65.
- Molander, E., Alehagen, S. and Bertero, C.M., 2010. Routine ultrasound examination during pregnancy: a world of possibilities. *Midwifery*, 26(1): 18-26.
- Montis, S. et al., 2010. Counseling and informed consent: the experience in a pediatric cardiology unit. How to communicate a pathological diagnosis. *Pediatr Med Chir*, 32(5): 206-10.
- Märker-Hermann, E. and Fischer-Betz, R., 2010. Rheumatic diseases and pregnancy. *Curr Opin Obstet Gynecol*, 22(6): 458-65.
- Nakayama-Furukawa, F., Takigawa, M., Iwatsuki, K., Sato, N. and Sato, H., 1994. Hydrocephalus in two female siblings with neonatal lupus erythematosus. *Arch Dermatol*, 130(9): 1210-2.
- Neiman, A.R., Lee, L.A., Weston, W.L. and Buyon, J.P., 2000. Cutaneous manifestations of neonatal lupus without heart block: characteristics of mothers and children enrolled in a national registry. *J Pediatr*, 137(5): 674-80.
- Neri, F. et al., 2004. Neuropsychological development of children born to patients with systemic lupus erythematosus. *Lupus*, 13(10): 805-11.
- Nisole, S., Stoye, J.P. and Salib, A., 2005. TRIM family proteins: retroviral restriction and antiviral defence. *Nat Rev Microbiol*, 3(10): 799-808.
- O'Brien, C.A. and Wolin, S.L., 1994. A possible role for the 60-kD Ro autoantigen in a discard pathway for defective 5S rRNA precursors. *Genes Dev*, 8(23): 2891-903.
- O'Brien, E.T., Quenby, S. and Lavender, T., 2010. Women's views of high risk pregnancy under threat of preterm birth. *Sex Reprod Healthc*, 1(3): 79-84.
- Paladini, D., Calabr , R., Palmieri, S. and D'Andrea, T., 1993. Prenatal diagnosis of congenital heart disease and fetal karyotyping. *Obstet Gynecol*, 81(5 (Pt 1)): 679-82.
- Petersen, J. and Jahn, A., 2008. Suspicious findings in antenatal care and their implications from the mothers' perspective: a prospective study in Germany. *Birth*, 35(1): 41-9.
- Petri, M., 1998. Pregnancy in SLE. *Baillieres Clin Rheumatol*, 12(3): 449-76.
- Pisoni, C.N. et al., 2010. Failure of intravenous immunoglobulin to prevent congenital heart block: Findings of a multicenter, prospective, observational study. *Arthritis Rheum*, 62(4): 1147-52.
- Porter, S. and Birt, A., 2001. Is Traumatic Memory Special? A Comparison of Traumatic Memory Characteristics with Memory for Other Emotional Life Experiences. *Applied Cognitive Psychology*, 15 101-117.
- Pozzo, M.L., Brusati, V. and Cetin, I., 2010. Clinical relationship and psychological experience of hospitalization in "high-risk" pregnancy. *Eur J Obstet Gynecol Reprod Biol*, 149(2): 136-42.

- Press, J. et al., 1996. Long-term outcome of mothers of children with complete congenital heart block. *Am J Med*, 100(3): 328-32.
- Ramos-Casals, M. et al., 2008. Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine (Baltimore)*, 87(4): 210-9.
- Rein, A.J. et al., 2009. Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro-SSB/La antibodies: a prospective, observational, fetal kinetocardiogram-based study. *Circulation*, 119(14): 1867-72.
- Reymond, A. et al., 2001. The tripartite motif family identifies cell compartments. *EMBO J*, 20(9): 2140-51.
- Rivera, T.L. et al., 2009. Disease progression in mothers of children enrolled in the Research Registry for Neonatal Lupus. *Ann Rheum Dis*, 68(6): 828-35.
- Rosenberg, K.B. et al., 2010. Referral for fetal echocardiography is associated with increased maternal anxiety. *J Psychosom Obstet Gynaecol*, 31(2): 60-9.
- Rosenthal, D., Druzin, M., Chin, C. and Dubin, A., 1998. A new therapeutic approach to the fetus with congenital complete heart block: preemptive, targeted therapy with dexamethasone. *Obstet Gynecol*, 92(4 Pt 2): 689-91.
- Ross, G., Sammaritano, L., Nass, R. and Lockshin, M., 2003. Effects of mothers' autoimmune disease during pregnancy on learning disabilities and hand preference in their children. *Arch Pediatr Adolesc Med*, 157(4): 397-402.
- Ruffatti, A. et al., 2012. A combination therapy to treat second-degree anti-Ro/La-related congenital heart block: a strategy to avoid stable third-degree heart block? *Lupus*, 21(6): 666-71.
- Saar, P., Hermann, W. and Müller-Ladner, U., 2006. Connective tissue diseases and pregnancy. *Rheumatology (Oxford)*, 45 Suppl 3: iii30-2.
- Saleeb, S., Copel, J., Friedman, D. and Buyon, J.P., 1999. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the research registry for neonatal lupus. *Arthritis Rheum*, 42(11): 2335-45.
- Salomonsson, S. et al., 2002. A serologic marker for fetal risk of congenital heart block. *Arthritis Rheum*, 46(5): 1233-41.
- Salomonsson, S. et al., 2011. A population-based investigation of the autoantibody profile in mothers of children with atrioventricular block. *Scand J Immunol*, 74(5): 511-7.
- Salomonsson, S. et al., 2005. Ro/SSA autoantibodies directly bind cardiomyocytes, disturb calcium homeostasis, and mediate congenital heart block. *J Exp Med*, 201(1): 11-7.
- Sandelowski, M. and Jones, L.C., 1996. Couples' evaluations of foreknowledge of fetal impairment. *Clin Nurs Res*, 5(1): 81-96.
- SBU, 2006. Metoder för tidig fosterdiagnostik. Statens beredning för medicinsk utvärdering, Stockholm.
- Schieppati, A., Henter, J.I., Daina, E. and Aperia, A., 2008. Why rare diseases are an important medical and social issue. *Lancet*, 371(9629): 2039-41.
- Schmidt, K.G., Ulmer, H.E., Silverman, N.H., Kleinman, C.S. and Copel, J.A., 1991. Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. *J Am Coll Cardiol*, 17(6): 1360-6.
- Selander, B., Cedergren, S. and Domanski, H., 1998. A case of severe neonatal lupus erythematosus without cardiac or cutaneous involvement. *Acta Paediatr*, 87(1): 105-7.

- Shanske, A.L., Bernstein, L. and Herzog, R., 2007. Chondrodysplasia punctata and maternal autoimmune disease: a new case and review of the literature. *Pediatrics*, 120(2): e436-41.
- Siddiqui, A. and Hägglöf, B., 2000. Does maternal prenatal attachment predict postnatal mother-infant interaction? *Early Hum Dev*, 59(1): 13-25.
- Silverman, E. and Jaeggi, E., 2010. Non-cardiac manifestations of neonatal lupus erythematosus. *Scand J Immunol*, 72(3): 223-5.
- Simkin, P., 1991. Just another day in a woman's life? Women's long-term perceptions of their first birth experience. Part I. *Birth*, 18(4): 203-10.
- Sklansky, M. et al., 2002. Maternal psychological impact of fetal echocardiography. *J Am Soc Echocardiogr*, 15(2): 159-66.
- Skomsvoll, J.F., Ostensen, M., Irgens, L.M. and Baste, V., 1998. Obstetrical and neonatal outcome in pregnant patients with rheumatic disease. *Scand J Rheumatol Suppl*, 107: 109-12.
- Solomon, D.G., Rupel, A. and Buyon, J.P., 2003. Birth order, gender and recurrence rate in autoantibody-associated congenital heart block: implications for pathogenesis and family counseling. *Lupus*, 12(8): 646-7.
- Sonesson, S.E., 2010. Diagnosing foetal atrioventricular heart blocks. *Scand J Immunol*, 72(3): 205-12.
- Sonesson, S.E., Salomonsson, S., Jacobsson, L.A., Bremme, K. and Wahren-Herlenius, M., 2004. Signs of first-degree heart block occur in one-third of fetuses of pregnant women with anti-SSA/Ro 52-kd antibodies. *Arthritis Rheum*, 50(4): 1253-61.
- Stern, D., 1998. *The motherhood constellation: a unified view of parent-infant psychotherapy*. Karnac Books, London.
- Stern, D. and Bruschiweiler-Stern, N., 1998. *The birth of a mother. How the motherhood experience changes you forever* Basic Books, New York.
- Strandberg, L.S. et al., 2010. Maternal MHC regulates generation of pathogenic antibodies and fetal MHC-encoded genes determine susceptibility in congenital heart block. *J Immunol*, 185(6): 3574-82.
- Theander, E. et al., 2001. Primary Sjögren's syndrome--treatment of fetal incomplete atrioventricular block with dexamethasone. *J Rheumatol*, 28(2): 373-6.
- Tincani, A. et al., 1998. Anticardiolipin and anti-beta 2glycoprotein I immunoassays in the diagnosis of antiphospholipid syndrome. *Clin Exp Rheumatol*, 16(4): 396-402.
- Tincani, A. et al., 2006. Autoimmunity and pregnancy: autoantibodies and pregnancy in rheumatic diseases. *Ann N Y Acad Sci*, 1069: 346-52.
- Tomblin, J.B. et al., 1997. Prevalence of specific language impairment in kindergarten children. *J Speech Lang Hear Res*, 40(6): 1245-60.
- Trucco, S.M. et al., 2011. Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. *J Am Coll Cardiol*, 57(6): 715-23.
- Wahren Herlenius, M., Sonesson, S.-E. and G, C.M.E., 2012. *Neonatal Lupus Erythematosus, Dubois' Lupus Erythematosus and Related Syndromes*. Saunders W B Co.
- Wahren, M., Solomin, L., Pettersson, I. and Isenberg, D., 1996. Autoantibody repertoire to Ro/SSA and La/SSB antigens in patients with primary and secondary Sjögren's syndrome. *J Autoimmun*, 9(4): 537-44.
- Waltuck, J. and Buyon, J.P., 1994. Autoantibody-associated congenital heart block: outcome in mothers and children. *Ann Intern Med*, 120(7): 544-51.

- van der Leij, J.N., Visser, G.H., Bink-Boelkens, M.T., Meilof, J.F. and Kallenberg, C.G., 1994. Successful outcome of pregnancy after treatment of maternal anti-Ro (SSA) antibodies with immunosuppressive therapy and plasmapheresis. *Prenat Diagn*, 14(10): 1003-7.
- Westerlund, M., 1994. Children with speech and language deviatons: A prospective longitudinalvepidemiological study of total age cohort of children living in Uppsala at 4,7 and 9 years of age, Uppsala University, Uppsala, 293 pp.
- Westerlund, M. and Sundelin, C., 2000. Can severe language disability be identified in three-year-olds? Evaluation of a routine screening procedure. *Acta Paediatr*, 89(1): 94-100.
- Weston, W.L., Morelli, J.G. and Lee, L.A., 1999. The clinical spectrum of anti-Ro-positive cutaneous neonatal lupus erythematosus. *J Am Acad Dermatol*, 40(5 Pt 1): 675-81.
- Wolach, B. et al., 1993. Aplastic anemia in neonatal lupus erythematosus. *Am J Dis Child*, 147(9): 941-4.
- Wolin, S.L. and Cedervall, T., 2002. The La protein. *Annu Rev Biochem*, 71: 375-403.
- Wolin, S.L. and Reinisch, K.M., 2006. The Ro 60 kDa autoantigen comes into focus: interpreting epitope mapping experiments on the basis of structure. *Autoimmun Rev*, 5(6): 367-72.
- Yee, W.H. and Sauve, R., 2007. What information do parents want from the antenatal consultation? *Paediatr Child Health*, 12(3): 191-6.
- Yoshikawa, N. et al., 2010. Neurodevelopment in the offspring of Japanese systemic lupus erythematosus patients. *Brain Dev*, 32(5): 390-5.
- Zeanah, C.H., Scheeringa, M. and Boris, N., 1994. Parenting styles and risks in the vulnerable infant. *Curr Opin Pediatr*, 6(4): 406-10.
- Zecca, G. et al., 2006. "All the rest is normal". A pilot study on the communication between physician and patient in prenatal diagnosis. *J Psychosom Obstet Gynaecol*, 27(3): 127-30.