Introduction
During the last decades there is an ongoing rise in the caesarean section rate. The caesarean rate in the Netherlands has been risen from 11.1% in 1999 up to 16.6% in 2015. World wide percentages of up to 40.5% are found in Latin America and the Caribbean and up to 64% in urban regions in China. Based on a WHO systematic review, increases in caesarean section rates up to 10-15% at the population level are associated with decreases in maternal, neonatal and infant mortality. Above this level, a further increase of the rate of caesarean section (CS) is no longer associated with reduced mortality. Due to an increase in the caesarean section rate more women experience the long term effects of a CS. Known long term effects are placenta accreta with an additional risk on hemorrhage and peri-partum hysterectomy, placental abruption and placenta previa. There is also an increased risk of uterine rupture, fetal growth restriction, preterm birth and possibly stillbirth. A pregnancy located in the caesarean scar is a rare but possibly life-threatening complication, with a prevalence of approximately 1 in 2000 pregnancies. Maternal long term complications are chronic pain and adhesions. Due to adhesions there is also an increased risk of bladder injury during subsequent CS or hysterectomy. Due to the increasing caesarean section rate and better image techniques, there is a renewed interest in the uterine caesarean scar in non pregnant women.

**Diagnosis**

The imaging of the caesarean scar in the non-pregnant uterus was first described in 1955 using hysterography and in 1961 a wedge defect detected by hysterography was described. With the introduction of the abdominal ultrasound hysterography was no longer used. In 1982 Burger reported the first prospective study with abdominal ultrasound on uterine caesarean scars in the post partum period. To be followed by Chen in 1990 using transvaginal ultrasound in both pregnant and non pregnant women. In 1999 saline infusion sonohysterography was first applied for the identification of caesarean scars followed by hysteroscopy in 2003. In a non-pregnant uterus the CS scar has different features on ultrasound, from a small hypoechoic line to an anechoic triangle or indentation filled with or without fluid. Monteagudo was the first to introduce the term niche for this feature in 2001. Other terms used include scar defect, deficient scar, diverticulum, pouch and isthmocele. This ultrasound feature is not seen after a vaginal birth. The most used definition for a niche evaluated by ultrasound is a triangular anechoic area at the site of the caesarean scar. Other definitions used are any visible defect or indentation, fluid within the scar and any thinning of the myometrium. The prevalence of a niche evaluated by ultrasound varies between 6.9%-84% due to different definition used, different populations investigated and different diagnostic methods used. Additionally, various studies focused on a selected group of women with gynaecologic symptoms or were small randomised controlled trials to study the effect of the technique used for uterine closure after CS. There is no gold standard for identifying a niche. Hysteroscopically niche evaluation was performed in symptomatic women only. The reported prevalence varied between 30-100%. A different prevalence of niches could also be caused by differences in time interval between the CS
and assessment of the uterine scar, varying from 48 hours to 15 years after a CS.\textsuperscript{26-28,33} At the time we designed the studies included in this thesis large prospective studies evaluating niche development (either by ultrasound, sonohysterography or hysteroscopy) and related symptomatology in a more or less random population after a CS were scarce.

**Relation with symptoms**
Several authors have suggested that niches are related to bleeding disorders, in particular post menstrual spotting, defined as brownish discharge/blood loss after the menstruation period has ended, or prolonged menstruation.\textsuperscript{27,36} Post menstrual spotting was postulated to be caused by retention in and delayed outflow of menstrual blood out of the uterine defect or due to the presence of fibrotic tissue below the niche or due to reduced uterine peristalsis. In addition in situ blood production by newly formed blood vessels in the niche could cause spotting too.\textsuperscript{36} Other reported symptoms are, chronic pelvic pain, dysmenorrhoea, dyspareunia, urologic symptoms and subfertility.\textsuperscript{27,36} At the time we designed the study the exact relation between niches and symptoms in a more or less random population after caesarean sections was not known. Additional risk factors on niche development and on the development of niche related symptoms were not fully elucidated. These factors are relevant for the development of predictive models and preventive strategies.

**Treatment**
As the caesarean scar and related symptoms become more established among patients and professionals there is a growing interest in treatment options. An effective treatment of niche related symptoms is a hysterectomy but this is accompanied by a risk of complications, loss of fertility and requires a substantial recovery period. Recent (robotic) laparoscopic and vaginal repair as well as hysteroscopic resection of the niche have been described to treat niche related symptoms.\textsuperscript{36,37} With a (robot) laparoscopic and vaginal repair the niche is cut out and the uterus is closed in layers. With a hysteroscopic niche resection the distal rim of the niche is resected to provide improvement of outflow of menstrual blood. Although the results of these surgical interventions seems promising with a low reported complication rate more research is needed to prove the effectiveness and to evaluate the outcome on fertility and subsequent pregnancies.\textsuperscript{36-38}
Chapter 1

Aim of the thesis

In view of these issues, this thesis aims to answer the following questions;

- What is the prevalence of niches after a caesarean section?
- How to measure a niche by ultrasound (comparing trans vaginal ultrasound with sonohysterography)
- Does a niche in the uterine caesarean scar change over time?
- What is the prevalence of niches during hysteroscopy?
- What are the features of a niche during hysteroscopy and how should it be reported?
- Is there a relationship between a niche and post menstrual spotting or urological symptoms?
- What are risk factors for niche development?
- What is the effect of various minimal invasive interventions on niche related symptoms?
- What is the effect of hysteroscopic niche resection in comparison to expectant management on post menstrual spotting?

Outline of this thesis

This thesis is structured into twelve chapters, outlined below:

Chapter two presents the result of a systematic review of the literature, providing an overview of the prevalence of niches, niche-related symptoms and risk factors for developing a niche.

Chapter three reports the results of a prospective cohort study evaluating the prevalence of a niche after a caesarean section by both transvaginal ultrasound and gel installation sonography and the relationship of niches with post menstrual spotting and urinary incontinence.

In chapter four results are presented of a proof of concept study, a longitudinal cohort study evaluating the changes of a niche by repeated ultrasound measurements during the first year after a caesarean section.

Chapter five shows the results of a prospective cohort study evaluating niches by hysteroscopy in women seeking hysteroscopic sterilisation

Chapter six describes a study including women with one previous caesarean section in order to identify risk factors and to develop a prognostic model for niche development.

Chapter seven contains a systematic review on minimal invasive therapy for niche related symptoms.
**Chapter eight** provides a study protocol for a multicenter randomised controlled trial to evaluate the effectiveness and cost effectiveness of a hysteroscopic resection of a niche, the HysNiche trial.

In **chapter nine** the results of the HysNiche trial are presented.

A summary in English and Dutch are given in **chapter ten**.

In **chapter eleven** the results of this thesis are discussed, clinical implications are addressed and implications for further research will be provided.
References


10. van Vugt RH. De latere gevolgen van de keizersnede, thesis 1966, Utrecht University, The Netherlands


