Early pregnancy challenges: study of caesarean scar pregnancy through a novel national surveillance platform and systematic reviews of priority questions in miscarriage management

by

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SYNOPSIS

This PhD developed a national network and research platform for the study of serious and uncommon disorders in early pregnancy: The UK Early Pregnancy Surveillance System (UKEPSS). Using the UKEPSS platform, with an early pregnancy network of 86 UK hospitals and Early Pregnancy Units (EPUs), a nation-wide prospective cohort study of caesarean scar pregnancy was performed.

Based on the findings of this study we recommend that;

- Women who have had a caesarean section delivery should be counselled about the risk of caesarean scar pregnancy (CSP).
- Women should be informed that the estimated UK incidence of CSP is 1 per 10 000 maternities. Age, smoking, parity and number of caesarean sections are strongly associated with an increased risk of developing a CSP.
- The most common presenting feature is vaginal bleeding. The mean gestation at presentation is 9 weeks (range 6 – 18 weeks).
- Transvaginal ultrasound scan is the most commonly used investigation for the diagnosis of CSP.
- Women should be counselled about the different treatment options for the management of CSP, including expectant, medical and surgical management, and the benefits and risks of each approach.
- Surgical management with dilatation and curettage is associated with a high success rate and early discharge and in the majority of cases should be considered as first line management.
- Treatment approach should be based on a shared management plan between the woman and the clinician.

Moreover, based on the findings of the second section of this thesis which comprises of systematic reviews in priority questions in miscarriage management, we suggest that;

- Women presenting with early pregnancy bleeding may benefit from progestogen treatment. Current evidence on the effectiveness of progestogens to reduce miscarriage is weak and a high quality randomised controlled trial is recommended to address this question. *Based on the findings of this review, funding was sought from the NIHR HTA programme, and we were successful in being awarded £1.8 million (co-applicant) to conduct a multi-centre randomised controlled trial (RCT): The **PRISM** Trial: **PR**ogesterone **I**n **S**pontaneous **M**iscarriage Trial.*

- Women with hydrosalpinx undergoing IVF treatment have an increased risk of miscarriage. Treatment with salpingectomy may reduce the risk of miscarriage. Further research is needed to assess the benefit of screening for hydrosalpinx in women with a history of recurrent miscarriage.

- Women of Black and Asian ethnicity appear to be at increased risk of miscarriage when compared to women of White ethnicity, a finding demonstrated in spontaneous and IVF conceived pregnancies. Further research is needed to understand the reasons for the observed difference to allow a targeted approach to investigations and management.

DEDICATION

I dedicate this thesis to my parents, Dr Maaly Harb and Mrs Mariam Martinez, whose unconditional love, and ever continuing guidance and support have enabled me to be where I am today

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ABBREVIATIONS

AEPU	Association of Early Pregnancy Units
BPSU	British Paediatric Surveillance Unit
CEMD	Confidential Enquiry into Maternal Deaths
CI	Confidence Interval
CS	Caesarean Section
CSP	Caesarean Scar Pregnancy
CRF	Case Report Form
EP-CSG	Early Pregnancy Clinical Studies Group
EPT	Ectopic Pregnancy Trust
EPU	Early Pregnancy Unit
HTA	Health Technology Assessment
IQR	Interquartile Range
MA	Miscarriage Association
MeSH	Medical Subject Heading
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NHS	National Health Service

NICE	National Institute of Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not Reported
OR	Odds Ratio
aOR	Adjusted Odds Ratio
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
RR	Relative Risk
SR	Systematic Review
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UKEPSS	United Kingdom Early Pregnancy Surveillance Service
UKOSS	United Kingdom Obstetric Surveillance System

National and International presentations from this thesis

- UKEPSS update. RCOG Annual Professional Development Conference. November 2014, UK. (Invited speaker)
- UKEPSS. Association of Early Pregnancy Units (AEPU) Annual conference, November 2014. UK. (Keynote speaker)
- The PRISM Trial. Gynaecological Visiting Society, October 2014, UK. (Invited speaker)
- Ethnicity and miscarriage: a large prospective observational study and meta-analysis. ASRM conference, Hawaii, October 2014. (Oral presentation)
- The effect of presence and management of hydrosalpinx on miscarriage in IVF ASRM conference. Hawaii, USA, October 2014. (Poster presentation)
- The UKEPSS project. Research and Development Showcase, Birmingham Women's Hospital. November 2013. (Invited speaker)
- UKEPSS: The United Kingdom Early Pregnancy Surveillance Service for uncommon disorders of early pregnancy**.** AEPU Conference. November 2013. (Invited speaker)
- UKEPSS. Early Pregnancy Meeting, Ectopic Pregnancy Trust**.** October 2013, Edinburgh, UK. (Invited speaker)
- The PRISM Trial. Early Pregnancy Meeting, Ectopic Pregnancy Trust**.** October 2013, Edinburgh, Scotland. (Invited speaker)

  Progestogen for the treatment of threatened miscarriage. AEPU Annual conference. November 2012. (Invited speaker)

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- Ethnicity and miscarriage: a large prospective observational study and meta-analysis.

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  Target: BMJ

- The effect of presence and management of hydrosalpinx on miscarriage in IVF.

  Al-Rshoud F; **Harb H**; Coomarasamy A.

  Target: BMJ

- Caesarean scar pregnancy: a systematic review and meta-analysis.

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CHAPTER 1: INTRODUCTION

INTRODUCTION

Early pregnancy complications are amongst the most common reasons for presentation to hospital in women during pregnancy. Approximately 210,000 (21%) early pregnancy complications occur in an estimated 1 million pregnancies per year in the UK. (1) These usually occur before 12 weeks gestation and include vaginal bleeding, miscarriage, ectopic pregnancies, pregnancies of unknown location, adnexal masses and molar pregnancies.

Any complication in pregnancy can be extremely distressing to a woman. For instance, miscarriage can result in substantial adverse psychological impact for women and studies have shown that the level of distress and the bereavement reaction associated with miscarriages can be equivalent to those of women who have suffered the stillbirth of a term baby. (1)

The most frequent complication of pregnancy is miscarriage, affecting one in five pregnancies. Another early pregnancy complication is ectopic pregnancy with an estimated incidence of 11 per 1000 pregnancies, and a maternal mortality of 0.2 per 1000 estimated ectopic pregnancies. About two thirds of these deaths are associated with substandard care.(2) Over the years the Confidential Enquiries into Maternal Deaths reports have consistently shown that young women in the UK continue to die in early pregnancy.(3) The triennial reports have found that these deaths are often related to common early pregnancy complications, but can also result from serious and rare disorders occurring in early pregnancy. These disorders are difficult to manage as they are rare and under-researched. For the care provider, it is important to be able to recognise early pregnancy complications and their consequences in

order that they may be able to counsel and treat women appropriately. Failure to manage early pregnancy problems appropriately can lead to a variety of adverse outcomes, including evacuation of a normal pregnancy, mismanagement of an ectopic pregnancy, maternal dissatisfaction and medico-legal action. (4)

AIMS

The primary aim of this PhD is to develop a novel approach for the study of rare early pregnancy disorders. Using this platform I will study caesarean scar pregnancy, a serious and uncommon early pregnancy condition, prioritised by a national body of clinicians, academics and patient representatives. Secondly, I will perform a number of systematic reviews to address priority questions in miscarriage management.

This thesis will therefore be divided into two sections;

Section 1: UKEPSS study of caesarean scar pregnancy

Section 2: Systematic reviews of priority questions in miscarriage management

SECTION 1: THE UNITED KINGDOM EARLY PREGNANCY SURVEILLANCE SERVICE CAESAREAN SCAR PREGNANCY STUDY

Objectives

1. Establish a national network of Early Pregnancy Units
2. Develop a national platform for the study of serious and uncommon conditions of early pregnancy: The United Kingdom Early Pregnancy Surveillance Service (UKEPSS)
3. Study the serious and rare condition of caesarean scar pregnancy using the UKEPSS platform

UKEPSS

The Confidential Enquiries into Maternal Deaths (CEMD) have consistently shown that women die in early pregnancy, often leaving behind a young family. The most recent MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) report listed 8 such deaths (between 2010 and 2012). (3) Atypical presentations or complications of early pregnancy problems led to these maternal deaths. Sub-standard care was reported in a majority of the cases.

The maternal deaths represent the tip of the iceberg. It is estimated that there are over 100 ‘near misses’ for every death. (5) Although collectively the conditions that result in deaths and near misses place a substantial burden on families and the NHS, individually they are uncommon. There is paucity in published evidence on the diagnosis, treatment and outcomes of these conditions. Hence, clinical practice is rarely based on reliable evidence.

Uncommon disorders are difficult to study because routine information sources are unreliable and comprehensive studies, such as the BEST survey of eclampsia in 1992 require a large collaboration to identify relatively few cases.(6) A national collaboration can enable high quality research to improve our knowledge and help us provide better care for women with these problems. UKOSS (UK Obstetric Surveillance System) (7) and BPSU (British Paediatric Surveillance Unit) (8) are examples of such national collaborations that have made enormous contributions to improving patient care. Research recommendations from these surveillance systems have been vital in guiding practice and improving patient care within the NHS. Since 2005, UKOSS has published over 30 definitive reports to guide practice on critical conditions such as H1N1v influenza in pregnancy, uterine rupture and eclampsia. Similarly, BPSU (British Paediatric Surveillance Unit) has generated over 160 research publications through a national reporting platform for rare conditions in paediatrics. BPSU surveys have informed policy on antenatal screening, identified the risks of faulty packaging of chemistry sets(9) and investigated concerns about vitamin K therapy,(10) water-births (11) and variant Creutzfeldt-Jakob (CJD) in British children. (12)

This PhD proposes a national network and research platform for early pregnancy and emergency gynaecological conditions: The UK Early Pregnancy Surveillance System (UKEPSS). UKEPSS will use well-established approaches similar to those of UKOSS and BPSU. The UK offers a unique setting to study early pregnancy problems as the country is served by dedicated Early Pregnancy Units (EPUs); in the rest of the

world, early pregnancy problems are generally managed in general gynaecological or emergency departments. (13)

CAESAREAN SCAR PREGNANCY SURVEILLANCE STUDY

Ectopic pregnancy is defined as the implantation of a pregnancy outside of the uterine cavity and can be broadly divided into two groups; tubal and non-tubal ectopics. Non-tubal ectopics are rare in incidence, and can implant in locations such as the ovary, cervix, in caesarean section scars or peritoneum.

Ectopic pregnancy remains a leading cause of maternal mortality in early pregnancy in the UK, with two thirds of these deaths attributed to atypical presentation and delayed diagnosis.

Ectopic pregnancy was therefore prioritised as the first UKEPSS surveillance study, focusing on the condition of caesarean scar pregnancy. This condition was prioritised by a national body of clinicians and patient representatives from the Association of Early Pregnancy Units, (14) the Early Pregnancy Clinical Studies Group,(15) the Miscarriage Association (16) and the Ectopic Pregnancy Trust (17).

Whilst the number of deliveries in NHS hospitals have decreased in the past year (from 671,255 in 2012-13, to 646,904 in 2013-2014), the NHS Maternity Statistics for England, 2013-14, have shown a rise in the caesarean section rate by 0.7 per cent, to 26.2 per cent or 166,081caesarean sections in 2013-14. Specifically, there has been an increase in the number of elective caesareans (2.5 per cent) while emergency caesarean rates are down 1.8 per cent. This continues the trend observed over recent years of increasing elective caesarean rates but a drop in the

emergency caesarean rates. (18)Women are routinely counselled about a number of complications that are associated with caesarean deliveries, however, one of the risks that clinicians and patients appear to be facing increasingly in recent years is that of caesarean scar pregnancy.

Caesarean scar pregnancy is a rare and serious condition, which can be mistaken for a cervical pregnancy or a miscarriage, with the consequence of delayed diagnosis and life-threatening haemorrhage. (19) The study will look at the presentation, diagnosis, key management strategies and outcomes associated with this condition.

The specific questions I will attempt to address are:

1. What is the incidence of the condition?
2. What are the presenting features of the condition?
3. How is the condition diagnosed?
4. What are the risk factors associated with caesarean scar pregnancy? For example, are age, ethnicity or number of previous caesarean sections associated with an increased risk of the condition
5. How is the condition typically managed?
6. What are the important variations in management?
7. What are the outcomes?
8. What are the factors associated with poor outcomes?

SECTION 2: SYSTEMATIC REVIEWS OF PRIORITY QUESTIONS IN MISCARRIAGE MANAGEMENT

The Royal College of Obstetricians and Gynaecologists(20) defines miscarriage as;

'..the spontaneous loss of pregnancy before the fetus reaches viability. The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation. It should be noted that advances in neonatal care have resulted in a small number of babies surviving birth before 24 weeks of gestation.'

Through systematic reviews of the literature and meta-analyses of available data, I aim to address the following questions:

PRIORITY QUESTION 1: PROGESTOGEN FOR THE TREATMENT OF THREATENED MISCARRIAGE

Objectives

1. To determine the effectiveness of progestogens to reduce miscarriage in women presenting with early pregnancy bleeding
2. To identify adverse effects associated with progestogen use

Background

Threatened miscarriage is a very common first-trimester problem occurring in up to one-third of pregnancies. (13) This is a clinical diagnosis defined as vaginal bleeding

in the first trimester with or without abdominal pain.

One in 5 pregnancies miscarry. Early pregnancy loss accounts for over 50,000 admissions in the UK annually. (2) Miscarriage has the potential to cause both psychological and physical harm, including severe haemorrhage, infection, perforation of the womb during surgery for miscarriage, and occasionally death. (1;21;22)

In December 2012, the National Institute of Health and Care Excellence (NICE) launched a national guideline on “Ectopic pregnancy and Miscarriage” (CG154) (2) in which they called for a key clinical trial on the effects of progesterone in preventing miscarriage in women with early pregnancy bleeding, stating “A very large multicentre randomised controlled trial of women treated with either progesterone/progestogen or placebo should be conducted.” The aim of this chapter is to evaluate the effectiveness of progestogen treatment to reduce miscarriage by systematically reviewing trials of the use of progestogens in women with early pregnancy bleeding.

PRIORITY QUESTION 2: THE EFFECT OF PRESENCE AND MANAGEMENT OF HYDROSALPINX ON MISCARRIAGE RISK

Objectives

1. To determine the relationship between presence of hydrosalpinx and miscarriage
2. To evaluate the benefit of management of hydrosalpinx in reducing miscarriage risk

Background

Hydrosalpinx is a fluid-filled distension of the fallopian tube in the presence of distal tubal occlusion. The incidence of hydrosalpinx within infertile women is between 10 to 13% when diagnosed by ultrasound. This figure increases to 30% with the use of hysterosalpingogram or laparoscopy. (23) The most common pathogen associated with tubal damage is Chlamydia trachomatis. In vitro fertilization was first introduced as a method to overcome tubal infertility. (24)

It has been established that the presence of hydrosalpinx is associated with lower implantation and pregnancy rates.(25-27) Moreover, studies have demonstrated that treatment for hydrosalpinx can improve clinical pregnancy and live birth rate. (28;29) However, the question whether hydrosalpinx has a detrimental effect on an already established pregnancy, that is, when an intrauterine pregnancy is seen on ultrasonography is yet to be addressed. Moreover, it is not known whether treatment is beneficial in reducing miscarriage risk in these women. The aim of this review is to assess the effect of the presence and treatment of hydrosalpinx on miscarriage rate.

PRIORITY QUESTION 3: THE EFFECT OF ETHNICITY ON MISCARRIAGE

Objectives

1. To determine the relationship between ethnicity and miscarriage risk
2. To identify potentially at risk groups

The most common cause of early miscarriages is chromosomal abnormalities, occurring in about half of all early miscarriages. (30) Other factors associated with miscarriage risk include female age, anti-phospholipid syndrome (APS), previous miscarriage, thrombophilia, infection and uterine anomalies. (31-34) A link between ethnicity and miscarriage risk has been previously suggested. (35) Ethnicity has been associated with many adverse pregnancy outcomes. For instance, spontaneous preterm birth and fetal growth restriction have been shown to differ significantly in women of different ethnic backgrounds. (36-38)

No reviews to date have evaluated the effect of ethnicity on miscarriage. The aim of this chapter is to systematically review studies of ethnicity and pregnancy outcomes in early pregnancy.

Table 1. Summary of chapters included in this thesis

Chapter number	Title	Population	Intervention	Comparison or reference standard	Outcome (s)	Research Design
SECTION 1: The UK Early Pregnancy Surveillance Service study of caesarean scar pregnancy						
2	Establishing the UKEPSS network	Early Pregnancy units	Develop an early pregnancy network	None	Number and distribution of EPUs	A national network of Early Pregnancy Units
3	Ectopic pregnancy in a caesarean scar: a systematic review	Women with caesarean scar pregnancy	Surgical management	Expectant and Medical management	Successful treatment of CSP Complications	Systematic review and meta-analysis
4	Caesarean scar pregnancy surveillance methodology	Early Pregnancy Units Women with caesarean scar pregnancy	Development of the methodology for the study of caesaraen scar pregnancy using a national research platform			A national surveillance platform for the study of serious and uncommon early pregnancy disorders
5	Surveillance findings	Women with caesarean scar pregnancy	Expectant, medical or surgical treatment	Women with no CSP Expectant vs Medical vs Surgical	Successful treatment of CSP Complications Time to discharge	Cohort study
SECTION 2: Systematic reviews of priority questions in miscarriage management						
6	Progestogen for the treatment of threatened miscarriage	Women presenting with early pregnancy bleeding	Progestogen	Placebo or no treatment	Miscarriage	Systematic review and meta-analysis Survey
7	The effect of presence and management of hydrosalpinx on miscarriage	Women with hydrosalpinx undergoing IVF treatment	Salpingectomy or tubal clipping	Women without hydrosalpinx undergoing IVF No treatment	Miscarriage	Systematic review and meta-analysis
8	Ethnicity and miscarriage	Women of Black and Asian ethnicity	None	Women of white ethnicity	Miscarriage	Cohort study Systematic review and meta-analysis

SECTION 1:

UKEPSS CAESAREAN SCAR PREGNANCY

SURVEILLANCE STUDY

CHAPTER 2

ESTABLISHING THE UNITED KINGDOM EARLY PREGNANCY SURVEILLANCE SERVICE (UKEPSS)

OBJECTIVES

1. Identify the number and geographical distribution of Early Pregnancy Units (EPUs) serving the UK
2. Establish a national network of Early Pregnancy Units
3. Develop the methodology for the study of serious and uncommon conditions of early pregnancy units through a national surveillance platform (UKEPSS)

ESTABLISHING THE UKEPSS NETWORK

Background

Early pregnancy care has undergone radical changes over the years. The wide use of ultrasonography and the introduction of early pregnancy units (EPU) has brought about a shift from the inpatient admission of women with early pregnancy problems to general gynaecological wards, to outpatient management in specialist clinics. Early pregnancy assessment units have been established to facilitate the streamlining of patient care and to provide an effective service for the management of early pregnancy disorders. Women who are found to have normal pregnancies are given reassurance, whilst those diagnosed with complications such as an ectopic pregnancy or miscarriage are given counselling and are managed as appropriate. (2;13;39)

The earliest reported established Early Pregnancy Assessment Unit was in 1991 in the United Kingdom. It demonstrated an improvement in the quality of care, whilst reducing the number of admissions and average length of stay with significant cost

savings.(13) For example, the administration of intravenous fluids and anti-emetics in an outpatient clinic setting has reduced the need for women having to be hospitalised for supportive treatment. Moreover, EPU, which are often lead by nurse specialists offer a setting for psychological support and follow up.

Early pregnancy care has been revolutionised by the incorporation of ultrasound examination allowing women with ectopic pregnancy and other early pregnancy disorders to be assessed and followed up without the need for immediate intervention or admission. (40) Scanning can be performed by trained gynaecologists, sonographers and specialist nurses, and the setting also provides supervised training opportunities for trainees and nurses.

There is currently a lack of accurate information on the number and distribution of EPUs in the UK. The structure of the units varies from one unit to another and across regions. An overview of the EPUs registered with the Association of Early Pregnancy Units (AEPU) shows regional variations, with large numbers in the South East but comparatively few in the North Eastern areas. It is, therefore, not clear if access to EPU services is adequate across the regions, and what impact this may have on clinical outcomes. The information on the distribution of EPUs may facilitate service planning and policy, and may improve outcomes by identifying regions that require investment. Due to constant changes in practice and emerging evidence, a national network of early pregnancy units could facilitate the rapid dissemination and uptake of guidelines and recommendations, including those developed through UKEPSS studies.

Building the network

I used multiple methods to identify and invite EPUs to join the UKEPSS network. These included:

- Approaching units on the AEPU registry
- Direct communication with all NHS hospitals in the UK
- Contact via Early Pregnancy Clinical Studies Group (EPCSG), Miscarriage Association (MA) and Early Pregnancy Trust (EPT).
- Announcement at the national AEPU conferences (2012, 2013, 2014)
- Self-registration through UKEPSS website
- Contact through obstetric units (on the UK Obstetric Surveillance System [UKOSS] network)

Eighty six UK Early Pregnancy Units (EPUs) have registered with UKEPSS (Figure 1). Each EPU is represented within the UKEPSS network by a nominated clinician, nurse and a sonographer, and there are currently 133 early pregnancy practitioners registered and active in the participation with UKEPSS. The UKEPSS Network collected details of EPUs in the UK with names of lead clinicians, nurses and sonographers. This information can be used nationally by service planners and policy makers, for instance, the Department of Health to gather data on geographical spread of early pregnancy services. One of the anticipated outputs of the UKEPSS network is the rapid dissemination of guidelines and uptake of evidence, which can have the potential to improve care and outcomes for patients. Details of the network are made available on the UKEPSS website (http://www.birmingham.ac.uk/ukepss)

for use by clinicians, researchers and patients. It is anticipated that the UKEPSS Network will be an enduring legacy and a platform for future research beyond the PhD programme.

Scotland
Aberdeen Maternity Hospital Early Pregnancy Services
Ayrshire Maternity Unit, University Hospital Crosshouse
Dr Gray's Hospital (Elgin), NHS Grampian
Forth Valley Royal Hospital
Ninewells Hospital Dundee
Pregnancy Support Centre, Edinburgh
The MRC Centre for Reproductive Health, University of Edinburgh

North and North East
Bradford Teaching Hospitals NHS Trust
Calderdale & Huddersfield NHS Foundation Trust
Harrogate District Hospital EPAU
LIFE Newcastle Hospitals NHS Foundation Trust
Newcastle upon Tyne Hospitals NHS Trust
North Tyneside General Hospital
QE Gateshead Health Foundation Trust
St James University Hospital EPU
Sunderland Royal Hospital
University Hospital of North Durham
York Hospital EPAU

North West
Blackpool Teaching Hospitals NHS Trust
Blackpool Victoria Hospital EPAU
Central Manchester University Hospitals
Countess of Chester NHS Foundation Trust
East Lancashire Hospitals Trust, Burnley General EPAU/GAU
ELHT EPAU/Lancashire Womens Hospital
Liverpool Women's NHS Foundation Trust
Maternity Unit, Cumberland Infirmary
North Cumbria University Hospitals NHS Trust
Pennine Acute Hospitals NHS Trust
Preston Lancashire Teaching Hospitals NHS Foundation Trust
Southport & Ormskirk NHS Trust
St Helens & Knowsley Hospital/Whiston Hospital Whiston
St Mary's Hospital, Manchester
Southport & Ormskirk NHS Trust
West Cumberland Hospital, Whitehaven, Cumbria
Whiston Hospital
Wrightington, Wigan and Leigh Foundation NHS Trust

Northern Ireland
Belfast Health and Social Care Trust
Ulster Hospital, Dundonald

Wales
Princess Of Wales Hospital

East Midlands and East Anglia
Bedford Hospital
EastDarant Valley Hospital
Luton & Dunstable Hospital
Milton Keynes General Hospital Trust EPU
Nottingham University Hospitals NHS Trust EPAU
Nurture Fertility, Nottingham University Hospitals NHS Trust
Rosie Hospital, Cambridge University Hospitals FT
Royal Berkshire Hospital
Royal Derby Hospital GAU
Peterborough City Hospital EPU

London and Southeast
Barts Health NHS Foundation Trust
Buckinghamshire Healthcare NHS Trust
Brighton and Sussex University Hospitals NHS Trust
Chelsea and Westminster Hospital
Colchester General Hospital
Conquest Hospital, East Sussex Healthcare
Darant Valley Hosiptal, Dartford, Kent
Epsom General Hospital Surrey
Royal Hampshire County Hospital EPU
Heatherwood Hospital EPU
Homerton Hospital EPAU, London
King's College Hospital NHS Foundation Trust
Kettering General Hospital
Newham General Hospital
North Middlesex University Hospital
Queen Charlotte's and Chelsea Hospital
Royal Berkshire Hospital
St Peters Hospital, Chertsey
University College Hospital, London
West Middlesex University Hospital EPAU
Whittington Hospital
Wexham Park Hospital, Slough

Southwest
Derriford Hospital Plymouth
Dorset County Hospital
Musgrove Park Hospital Taunton
St Michael's University Hospital
Princess Anne Hospital, Southampton
Poole Hospital EPU
Royal Devon & Exeter Hospital Centre For Womens Health
Salisbury NHS Foundation Trust EPU

UKEPSS

Figure 1. UK EARLY PREGNANCY SURVEILLANCE SERVICE NETWORK

DEVELOPMENT OF THE METHODOLOGY FOR SURVEILLANCE

UKEPSS collaboration

The development of the UKEPSS network was described earlier in this chapter. Each EPU member was provided with access to a secure online database to report data on the conditions under surveillance.

Monthly electronic cards (e-cards)

Cases are collected through monthly electronic cards (e-cards) emailed monthly to a nominated clinician, nurse and ultrasonographer in each participating EPU. The e-card asks the reporting clinician to indicate whether there has been a case of caesarean scar pregnancy in their unit using a simple tick box. It contains a “nothing to report” check box to positively verify there have not been any cases, which is important for determination of denominators and calculation of rates. The response is recorded on the Electronic Data Capture (EDC) system, which also identifies units which have not returned their cards. A reminder is sent after 7 days and in the situation where there is still no response, a follow-up email or telephone call will be made.

Gathering data using Case Report Forms (CRFs)

If a case is reported on e-card, the reporting practitioner is asked to complete an electronic case report form (CRF). The CRF asks for core information that is collected on all women and condition-specific information to confirm diagnosis, and

collect data on presentation, risk factors, treatment and outcomes. UKEPSS does not collect any personally identifiable information, such as names, addresses or hospital numbers. Reporting practitioners are asked to keep their own record of the names of women they have reported so that they can retrieve the case notes in case additional information is required. If a case is reported, but no CRF is completed and returned, 3 electronic reminders are sent, followed by two telephone reminders.

DEVELOPING THE DATA CAPTURE SYSTEM

UKOSS have successfully collected data for more than 30 studies using a paper based system; this system requires reporting clinicians to mail a monthly return card, which is received by a co-ordinating team who send out a case report form (CRF) for every positive case reported. The CRF then needs to be completed by reporting clinicians and once again returned to the UKOSS co-ordinating centre. For UKEPSS, this system was developed to an electronic data capture (EDC) system to facilitate the reporting process, and to achieve significant time and cost savings, as well as efficiency, and quality gains.

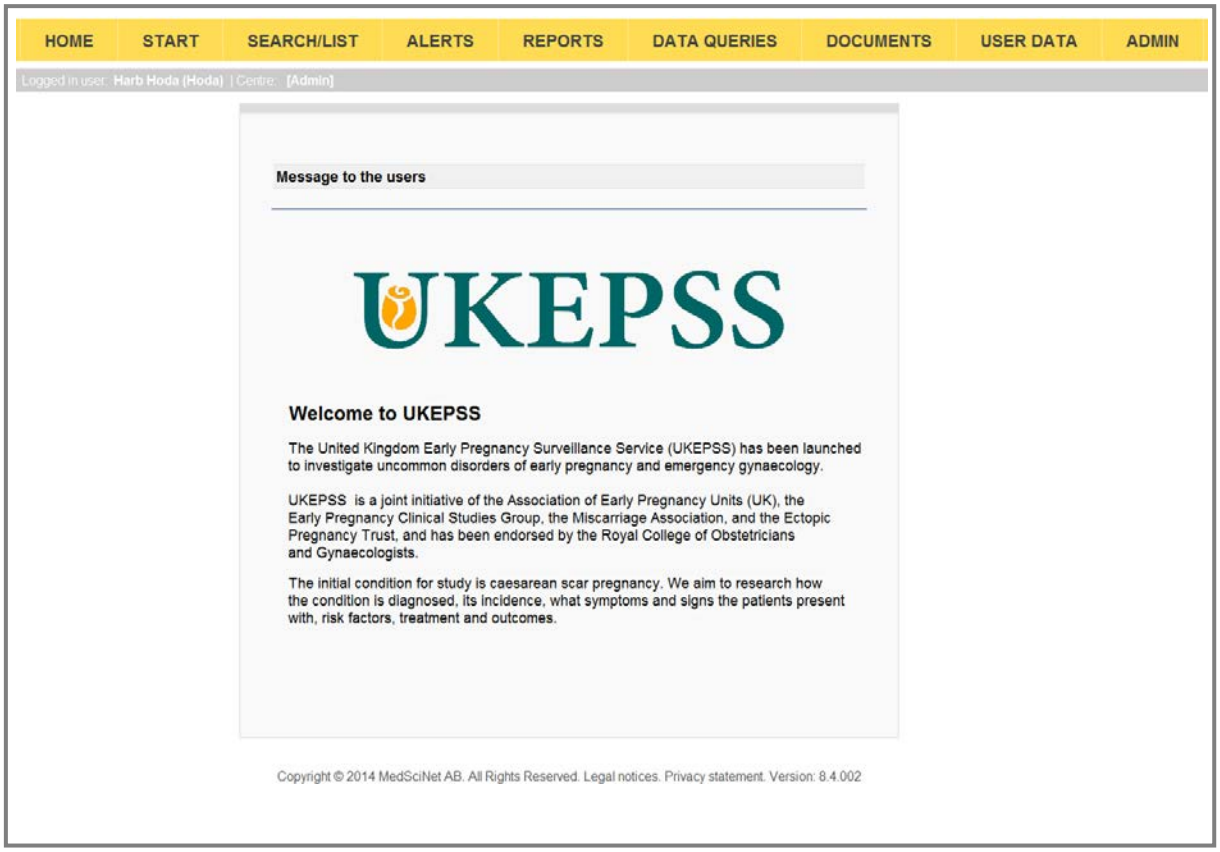
DESIGN

UKEPSS Database

The first step was to design the UKEPSS database, working closely with MedSciNet, a company based at King's College University (London) who have over 10 years' experience in supporting 38 clinical trials, 17 registries, and 9 resource centres, including international databases for the World Health Organisation (WHO). The database is an Electronic Data Capture (EDC) system that has been developed and delivered to ISO 9001:2000 standards and in compliance with FDA CRF21:11 requirements.

A unique interface (Figure 2) was developed to facilitate the registration of UKEPSS centres, communication and participation in UKEPSS studies. Predefined validation rules, custom rules and extensive repository of standard components were used to develop an efficient and secure database structure.

Figure 2. The UKEPSS database home page



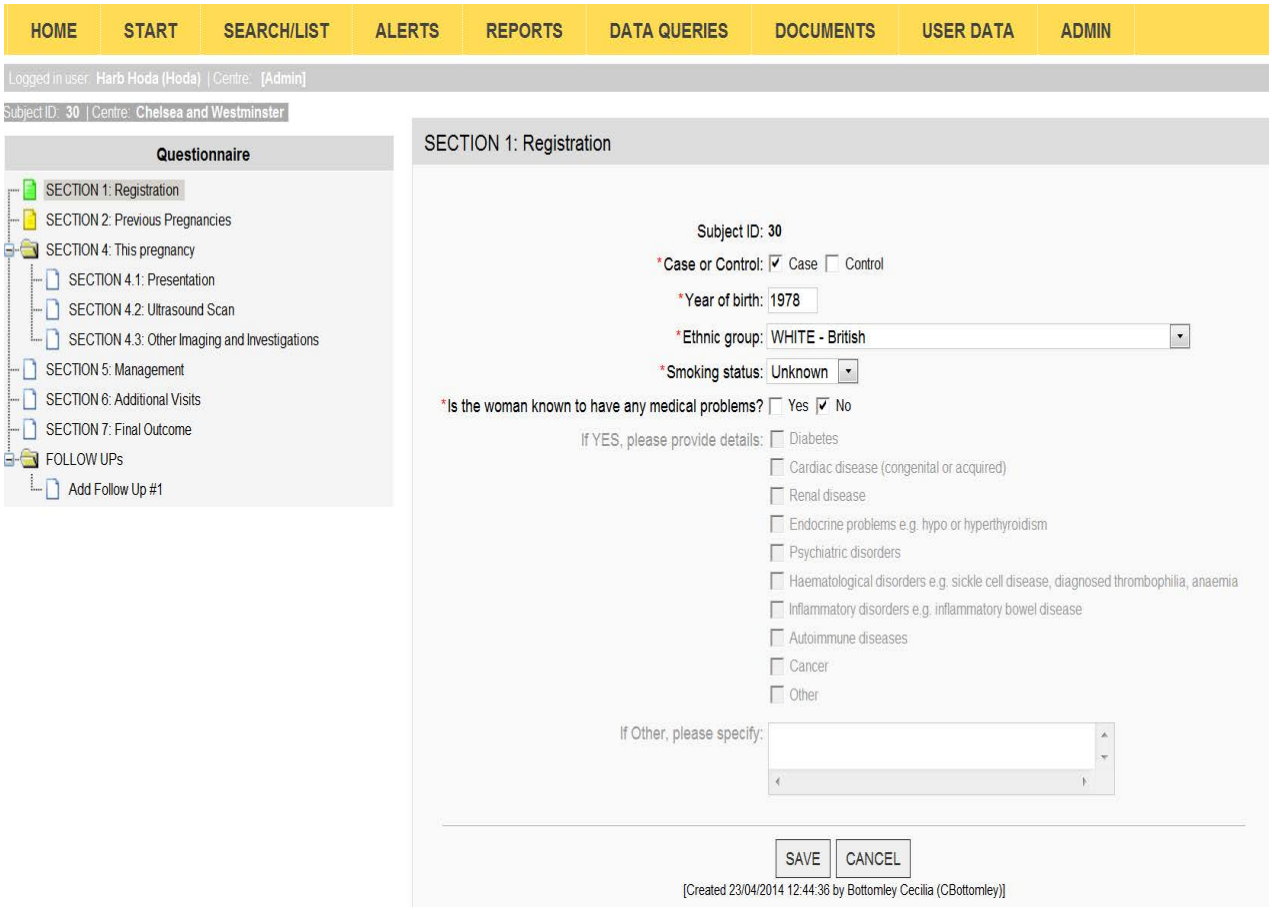
Case report form (CRF)

The next step was to create the electronic CRF (Figure 3) based on pre-defined research questions, which were developed by performing an extensive review of the literature. Moreover, each section was discussed in detail at the UKEPSS Study Steering Committee meeting held at the Royal College of Obstetricians and Gynaecologists. The group consists of early pregnancy clinicians, nurses and academics, such as the Director of UKOSS, Professor Marian Knight, who has

extensive experience in conducting studies of rare conditions. A list of the UKEPSS Study Steering Committee is included in the Appendix for reference. The UKEPSS Study Steering Committee approved the final version of the CRF. Numerous iterations of the electronic case report forms were created to develop a reporting system which is clear and simple to use.

A test site was created and circulated for use by participating clinicians to test the ease and functionality of the interface. After agreement, the database and study eCRF were launched on the 7th of February 2014 and the database (http://www.medscinet.com/ukepss/) was active for reporting over a 12 month surveillance period..

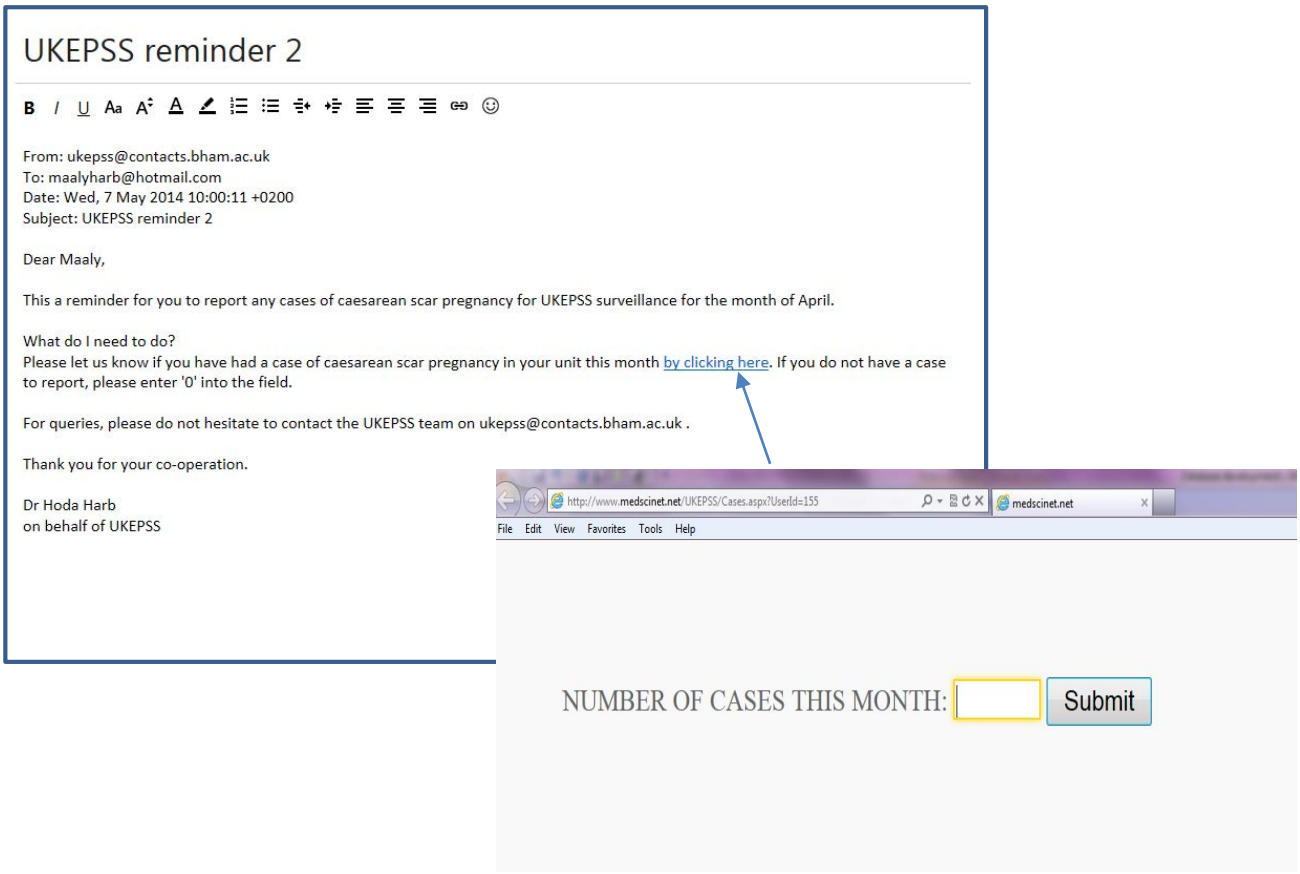
Figure 3. Caesarean scar pregnancy surveillance CRF



Data Collection

Every month UKEPSS electronic case notification cards are sent to nominated reporting clinicians in each hospital in the UK with a consultant-led early pregnancy unit, with a simple box to indicate whether they have seen a woman with CSP. They are also asked to return cards indicating a ‘‘nil report‘‘, in order that I could monitor card return rates and confirm the denominator to calculate the incidence rate. If a clinician returns a card indicating a case, they are then asked to complete an online data collection form asking for details on presentation, investigations, management and outcomes.

Figure 4. UKEPSS electronic case notification cards



Monitoring

To monitor monthly engagement, a function was been added to maintain global monitoring of response from units by returned cards. Centres that do not respond to the first UKEPSS e-card are sent a reminder one week later. The system then identifies those centres which have not responded to the reminder and a list is created of the units to contact by direct email or telephone.

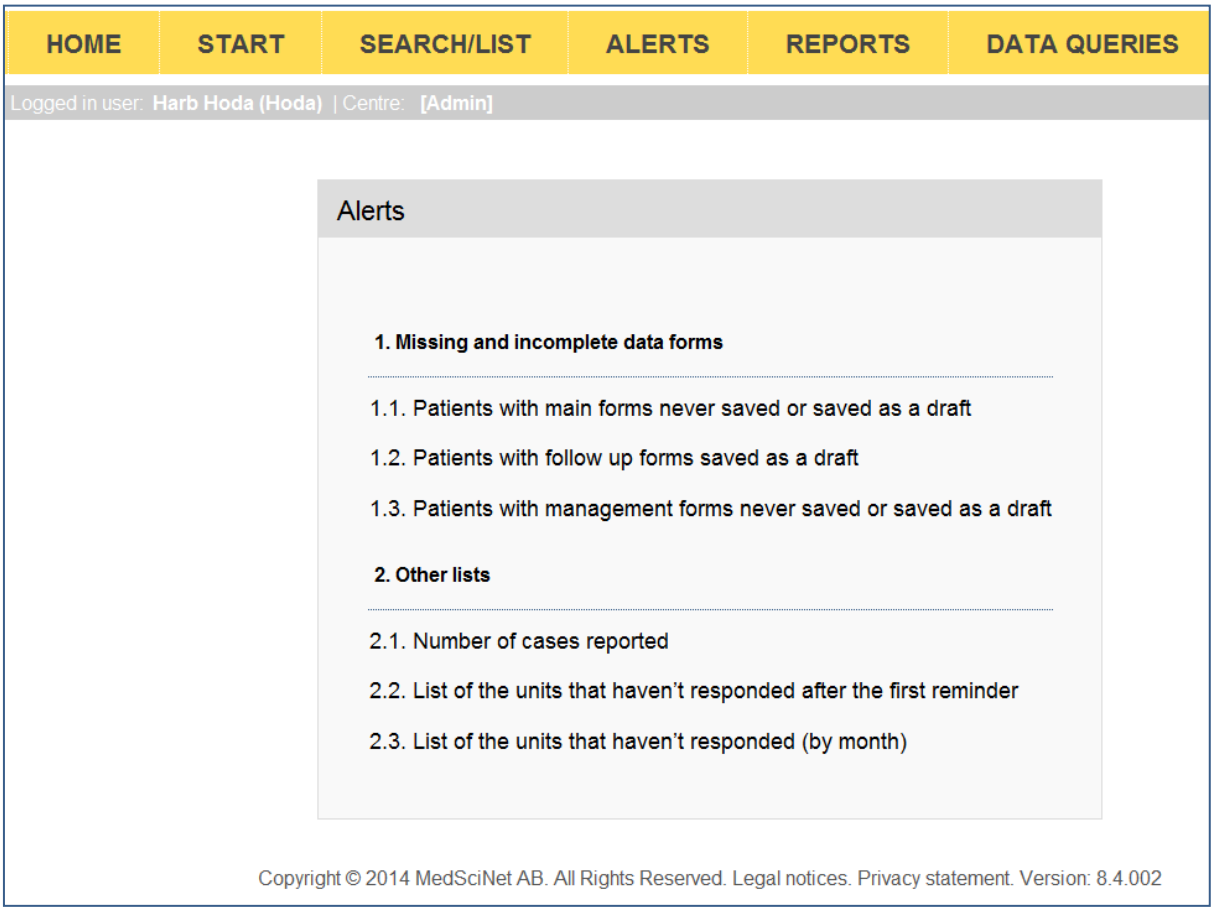
Data regulation

The secure online Electronic Data Capture (EDC) system has been developed and delivered to ISO 9001:2000 standards and in compliance with FDA CRF21:11 requirements.

Alert system for data completion

Alerts provide an efficient way for global monitoring. A comprehensive alert system was incorporated to detect incomplete data sets and missing forms (Figure 5).

Figure 5. Alert system for data completion

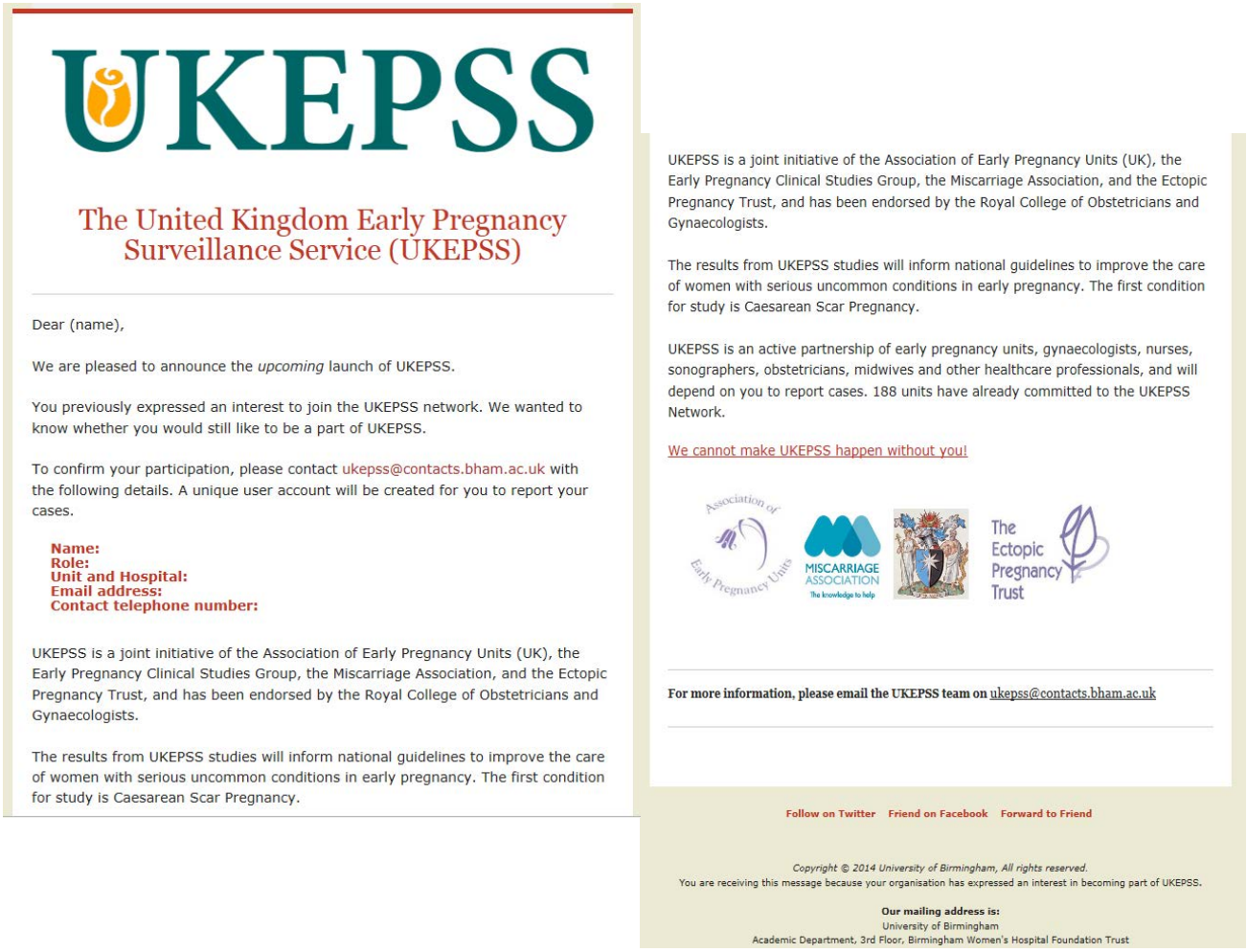


LAUNCH METHODOLOGY AND NETWORK ENGAGEMENT STRATEGIES

Multiple strategies were employed to introduce the national early pregnancy and gynaecology community to UKEPSS.

1. **Invitation emails:** Prior to launching, I designed e-leaflets (figure 6) which were disseminated to clinicians and EPAU units nationally.

Figure 6. UKEPSS e-leaflet invitation



UKEPSS

The United Kingdom Early Pregnancy Surveillance Service (UKEPSS)

Dear (name),

We are pleased to announce the *upcoming* launch of UKEPSS.

You previously expressed an interest to join the UKEPSS network. We wanted to know whether you would still like to be a part of UKEPSS.

To confirm your participation, please contact ukepss@contacts.bham.ac.uk with the following details. A unique user account will be created for you to report your cases.

Name:
Role:
Unit and Hospital:
Email address:
Contact telephone number:

UKEPSS is a joint initiative of the Association of Early Pregnancy Units (UK), the Early Pregnancy Clinical Studies Group, the Miscarriage Association, and the Ectopic Pregnancy Trust, and has been endorsed by the Royal College of Obstetricians and Gynaecologists.

The results from UKEPSS studies will inform national guidelines to improve the care of women with serious uncommon conditions in early pregnancy. The first condition for study is Caesarean Scar Pregnancy.

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The results from UKEPSS studies will inform national guidelines to improve the care of women with serious uncommon conditions in early pregnancy. The first condition for study is Caesarean Scar Pregnancy.

UKEPSS is an active partnership of early pregnancy units, gynaecologists, nurses, sonographers, obstetricians, midwives and other healthcare professionals, and will depend on you to report cases. 188 units have already committed to the UKEPSS Network.

We cannot make UKEPSS happen without you!

Association of Early Pregnancy Units · MISCARRIAGE ASSOCIATION The knowledge to help · The Ectopic Pregnancy Trust

For more information, please email the UKEPSS team on ukepss@contacts.bham.ac.uk

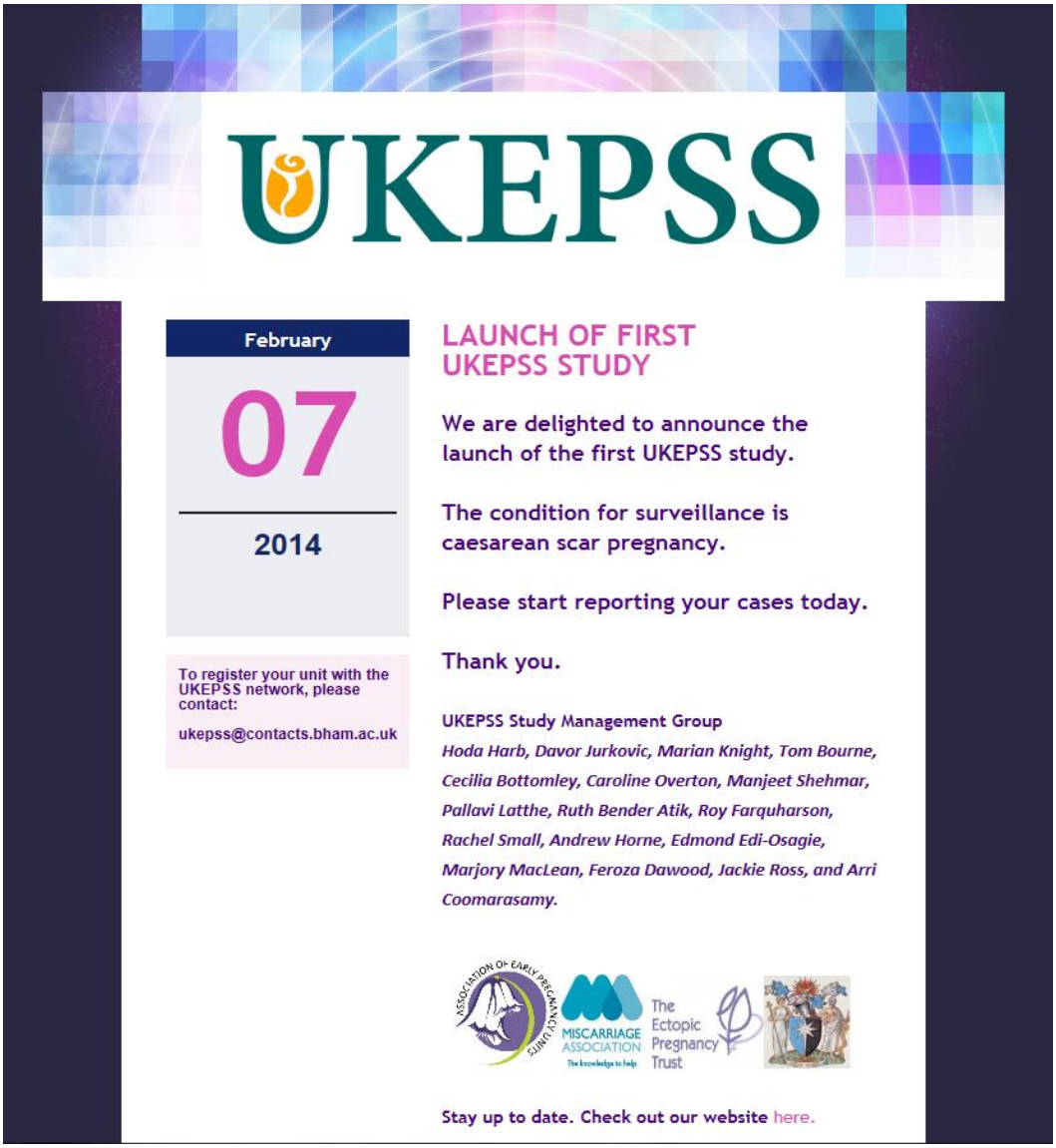
Follow on Twitter Friend on Facebook Forward to Friend

Our mailing address is:
University of Birmingham
Academic Department, 3rd Floor, Birmingham Women's Hospital Foundation Trust

2. Presentations at national and regional conferences: I presented at multiple local and national meetings including the Annual Association of Early Pregnancy Units Conference (2012, 2013, 2014) the Ectopic Pregnancy Trust, Early Pregnancy Meeting (Scotland), and the Birmingham Women's annual Research and Development meeting.

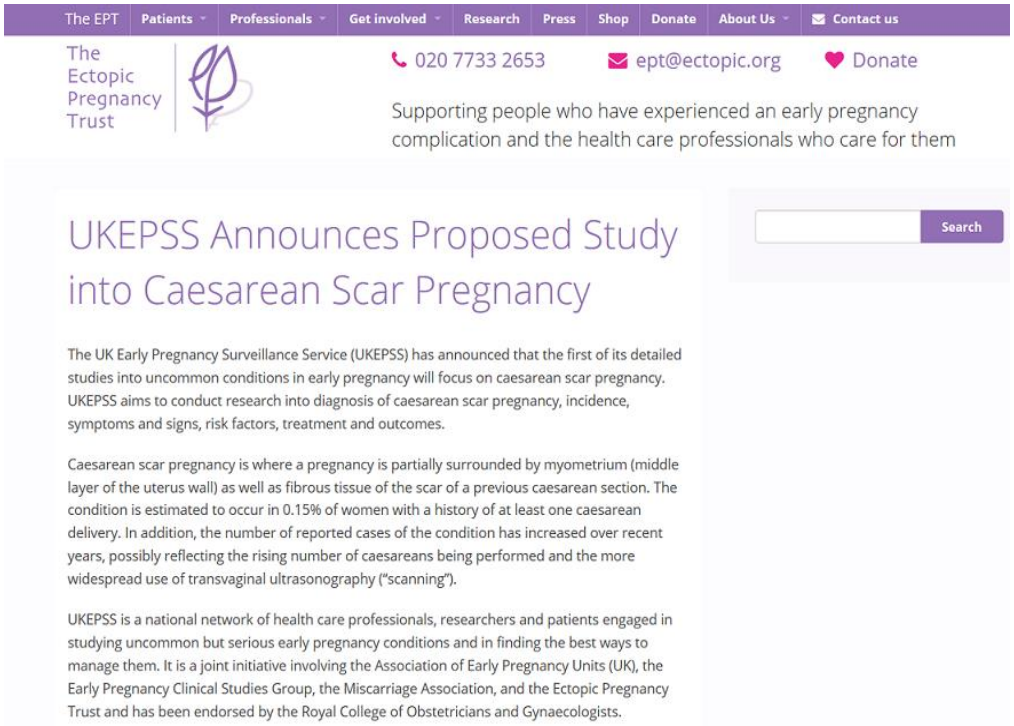
3. **Electronic launch announcement:** an e-flyer (figure 7) was sent to all contacts, registered units and obstetrics and gynaecology nurses and clinicians, identified through the AEPU registry, and by direct contact with every hospital in the UK with an obstetric and gynaecology unit.

Figure 7. UKEPSS electronic launch



4. **UKEPSS WEBSITE:** http://www.birmingham.ac.uk/ukepss, provides updates on study progress. Announcements were also made by supporting organisations online.

Figure 8. Ectopic Pregnancy Trust announcement of UKEPSS launch



5. Social media: A facebook page was set up to provide regular updates to participating units, followers and patients.

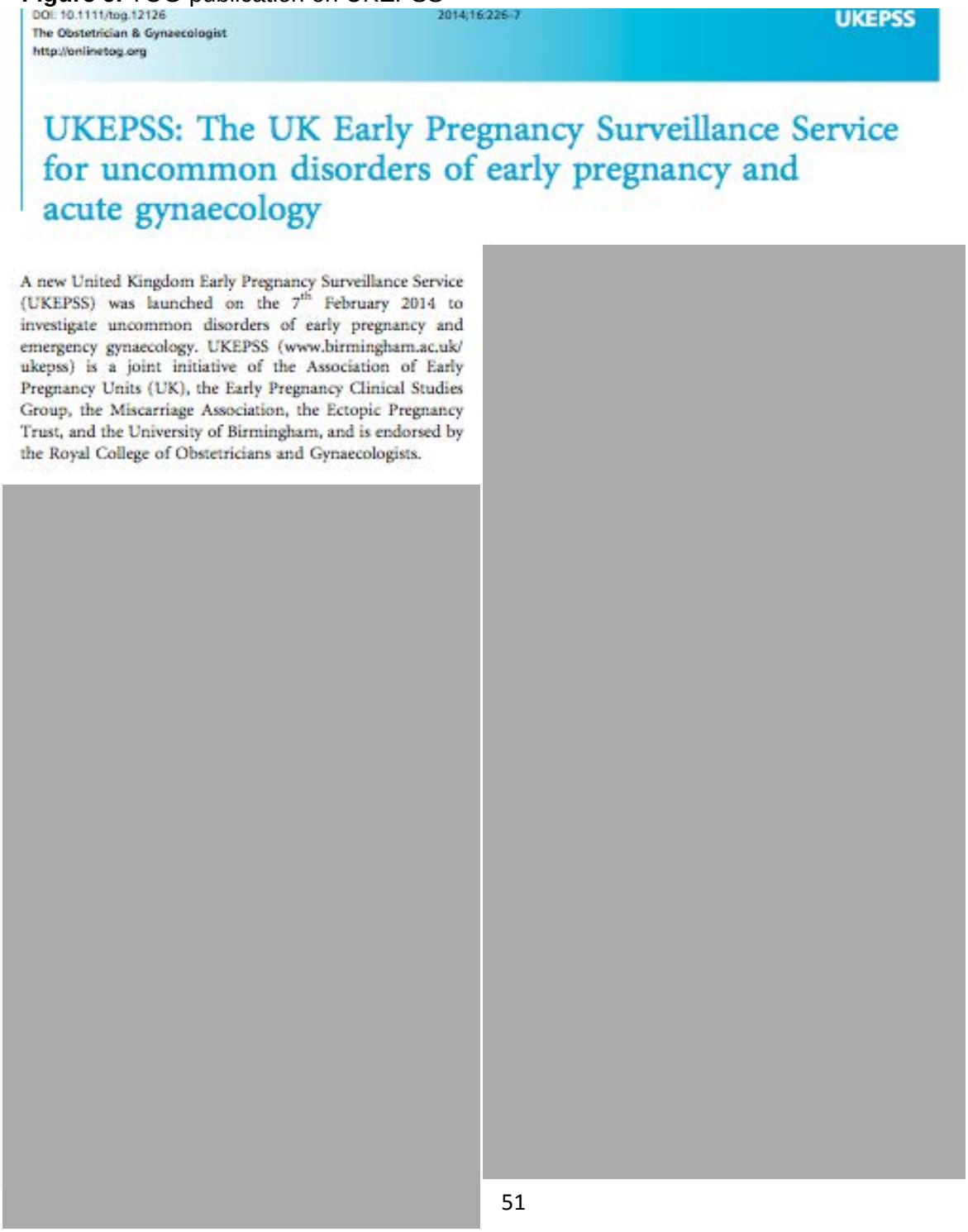
6. Direct email and telephone correspondence: Queries are promptly addressed using the UKEPSS central email (ukepss@contacts.bham.ac.uk)

7. TOG column: A commentary (figure 9) was submitted to The Obstetrician and Gynaecology (TOG) journal and was published in July 2014. Moreover, UKEPSS

has been invited to report biannually in the TOG journal. This will provide a key route to engagement of UK obstetrics and gynaecology clinicians and units, and will facilitate dissemination of findings nationally.

COMMENTARY

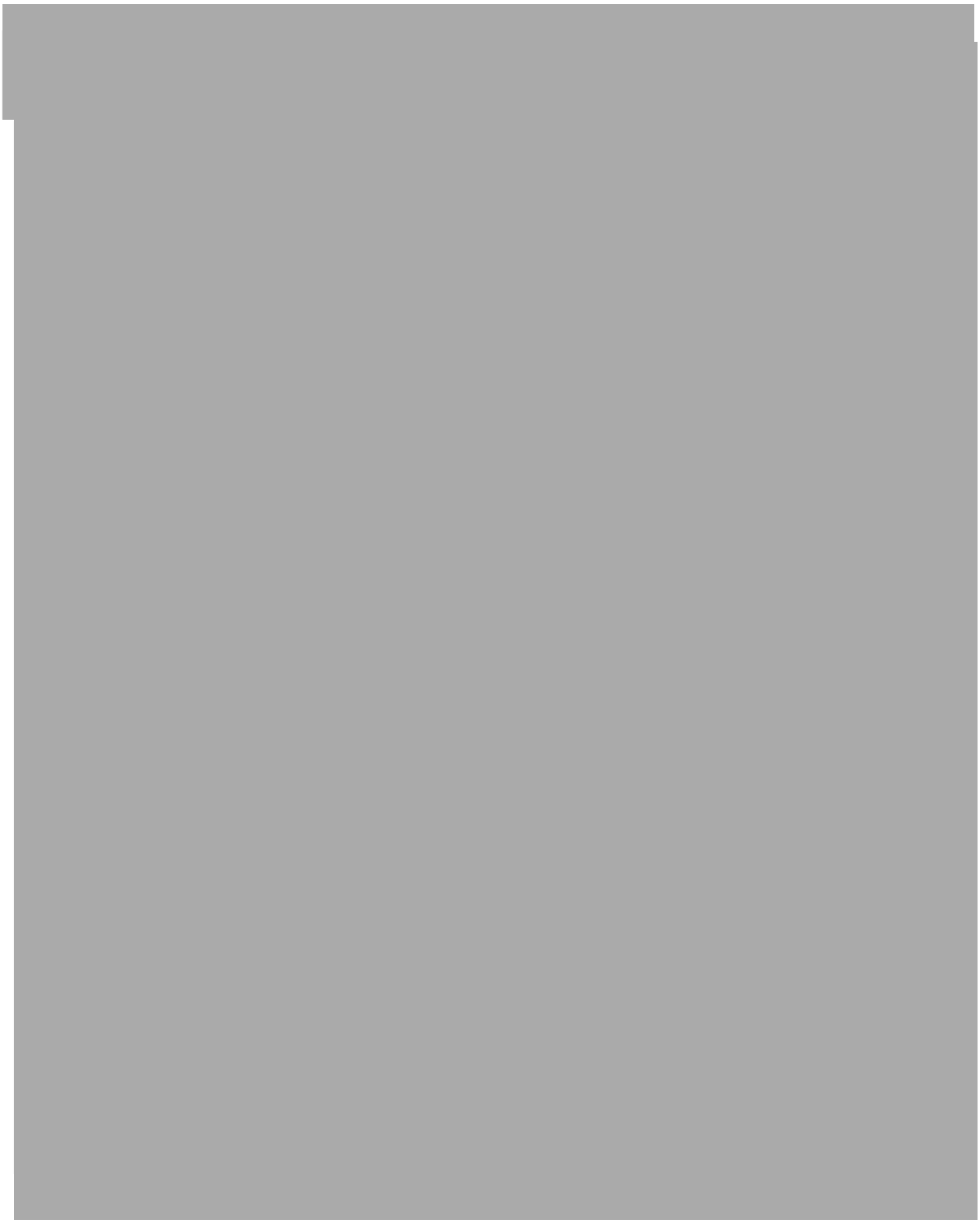
Figure 9. TOG publication on UKEPSS


DOI: 10.1111/tog.12126
The Obstetrician & Gynaecologist
http://onlinetog.org
2014;16:226–7

UKEPSS

UKEPSS: The UK Early Pregnancy Surveillance Service for uncommon disorders of early pregnancy and acute gynaecology

A new United Kingdom Early Pregnancy Surveillance Service (UKEPSS) was launched on the 7th February 2014 to investigate uncommon disorders of early pregnancy and emergency gynaecology. UKEPSS (www.birmingham.ac.uk/ukepss) is a joint initiative of the Association of Early Pregnancy Units (UK), the Early Pregnancy Clinical Studies Group, the Miscarriage Association, the Ectopic Pregnancy Trust, and the University of Birmingham, and is endorsed by the Royal College of Obstetricians and Gynaecologists.



CHAPTER 3

MANAGEMENT OF CAESAREAN SCAR PREGNANCY: A SYSTEMATIC REVIEW AND META-ANALYSIS

OBJECTIVES

1. To systematically review the literature to identify management approaches currently used for the treatment of caesarean scar pregnancy
2. To systematically review, and if possible, to meta-analyse data from the literature to determine the management approach associated with treatment success
3. To systematically review, and if possible, to meta-analyse data from the literature to identify adverse outcomes associated with each management approach
4. To use the findings of this review to develop the specific case report forms for the caesarean scar pregnancy surveillance study

ABSTRACT

Objective

To determine the effectiveness of the different management approaches for the treatment of caesarean scar pregnancy.

Methods

Studies were identified without language restrictions from MEDLINE (1966-2015), EMBASE (1980-2015), Cochrane Library, and manual searching of bibliographies of known primary and review articles. Studies were selected if treatment was given to women presenting with caesarean scar pregnancy and if studies reported outcomes of interest. Observational studies and case series were included in the absence of randomised trials. Data were extracted on study characteristics, quality and the outcome. Relative risks from individual studies were meta-analysed using random and fixed effects models. Heterogeneity was evaluated graphically using forest plots and statistically using the I^2 statistic.

Results

The search identified 12 case series comprising 274 women. Meta-analysis of these 12 studies showed that there was no difference between medical and surgical treatment for the outcome of successful treatment (RR 0.85, 95% CI: 0.70 to 1.04, p= 0.12; I2 = 12%, p=0.33). However, additional intervention was more likely to be performed in women undergoing medical management when compared to surgical management (RR 2.50, 95% CI: 1.10 to 5.65, p=0.03; I2= 15%, p=0.31). No

difference was found in complication rates including haemorrhage, need for emergency hysterectomy, persistent myometrial defects requiring repair, or rupture.

Conclusion

There is some evidence to suggest that surgical treatment is associated with less need for additional interventions, although no difference was found in overall treatment success. This review was limited by the quality, number and size of included studies. A prospective national surveillance may facilitate the study of this rare condition and enable recommendations for practice and further research.

INTRODUCTION

In a caesarean scar pregnancy (CSP), the ectopic pregnancy is partially or completely surrounded by myometrium and fibrous tissue of the scar of the prior lower uterine segment. The incidence of caesarean scar pregnancy is currently unknown; Jurkovic et al estimated a prevalence of 1:1800 in their local population, whilst in their case series, Seow at al found an incidence of 1: 1226 of all pregnancies. (19;41) The number of reported cases has increased over recent years, possibly reflecting the rising number of caesareans being performed and the more widespread use of transvaginal ultrasonography.

Differentiating between spontaneous miscarriage, cervical pregnancy and caesarean scar pregnancy can be difficult. Several potential predisposing factors have been suggested in the literature, including a history of dilatation and curettage, placental pathology, ectopic pregnancy, uterine closure and IVF require further investigation.(42) There are currently no validated criteria for the diagnosis of caesarean scar pregnancy.

There is currently no agreement on the management for caesarean scar pregnancies. Various treatment modalities for caesarean scar pregnancy have been described in the literature. There are three predominant treatment approaches: expectant, medical and surgical management. Delivery of a live term baby following expectant management has been reported in a number of cases but often with severe consequences to the mother, including massive haemorrhage and the need for a hysterectomy.(43) Medical management includes local or systemic

methotrexate, uterine artery embolization, and the injection of local potassium chloride in heterotopic pregnancies. Surgical treatment in the way of dilatation and curettage, hysteroscopic resection, laparoscopic excision and hysterectomy has been reported with varying success. A combined approach has also been described, such as the local administration of methotrexate followed by surgical dilatation and curettage. Other more novel techniques have also been reported, such as chemoembolization of the uterine arteries.

The aim of this review is to systematically review the available literature to assess outcomes associated with the various treatment approaches for the management of this condition. This information may be useful for the counselling and management of affected women.

METHODS

Identification of literature

The following electronic databases were searched: MEDLINE (1985 to January 2014), EMBASE (1985 to January 2015), Science Direct (1985 to January 2015), Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science (1985 to January 2015). A search strategy was carried out based on the following key words and/or medical subject heading (MeSH) terminology: ‘caesarean scar pregnancy’; ‘caesarean scar’; ‘ectopic pregnancy’, ‘caesarean scar complications’; ‘caesarean scar ectopic pregnancy’; ‘caesarean scar implantations’; pregnancy; caesarean; pregnancy; scar; ectopic; and ‘previous caesarean scar’, caesarean,

cesarean, pregnancy, scar, ectopic. Key words were combined using AND/OR. In addition, references from all identified articles were checked. If necessary, additional information was sought from the authors of the primary studies. The search was not restricted by language. The searches were conducted independently by me and two other reviewers, BW and MS.

STUDY SELECTION

Studies were selected if the target population were women reported to have a caesarean scar pregnancy. The primary outcome was successful treatment of caesarean scar pregnancy. Successful treatment was defined as resolution of caesarean scar pregnancy following primary management. Secondary outcomes included the need for additional interventions and complications. Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinized by two reviewers independently (HH and BW) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Secondly, final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publication, the most recent and complete versions were selected. We excluded case reports, commentaries and letters. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (MS). Data extraction was performed in duplicate by HH and BW.

Methodological quality assessment

All manuscripts meeting the selection criteria were assessed for their methodological quality. I used the MINORS checklist for the quality assessment of case series. The scale assesses for reliability, consistency and validity. A score between 0 and 2 is given for the adequacy of reporting; items are scored 0 if not reported, 1 where reported but inadequate, or 2 if reported and adequate. The overall ideal score is 16 for non-comparative studies and 24 for comparative studies.

Data extraction

I designed a data extraction form to extract relevant data. A second reviewer (BW) extracted data using the agreed form. Any discrepancies were resolved by discussion.

SYNTHESIS

I carried out relative effectiveness meta-analyses of treatment approaches using the Review Manager software (RevMan 5.3). Relative risks with 95% confidence intervals from each study were combined for meta-analysis using the Mantel-Haenszel method. The random-effect model was used as default for combining data from observational studies where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

Heterogeneity was assessed graphically using forest plot and statistically using I^2

test. To detect publication and related biases, I undertook funnel plot analysis using Egger's tests to evaluate for asymmetry.

RESULTS

The search strategy (figure 10) yielded 638 publications (634 from electronic searches; 4 from reference lists of relevant publications). There were no randomised controlled trials identified. From the title and abstract, 420 studies were excluded as it was clear that they did not fulfil the selection criteria or were in a foreign language. For the remaining 214 articles, I obtained full manuscripts, and following scrutiny of these, we excluded 202 studies for the following reasons: 178 were case reports, 16 were literature reviews or opinion articles, 6 studies contained duplicate data, and in 7 studies treatment was combined. Therefore the total number of studies included in this review is 12.

Study characteristics

The 12 studies (44-55) included a total of 274 women and were all case series. The study characteristics, including number of women, study design, age, caesarean section history, symptoms and signs at presentation, method of diagnosis, BhCG at presentation, primary treatment used, treatment success, complications, follow up duration and future pregnancy are summarized in Tables 2.1 and 2.2.

Quality of included studies

The quality of the included studies is summarised in Table 3.

Table 2.1. Characteristics of included studies of CSP showing patient demographics and presenting signs and symptoms

Author	Study Design	Population	Age (median)	Pregnancy history	Symptoms and gestation at presentation	Method of diagnosis and findings	BhCG at presentation (median)
Ben Nagi, 2007 **(n=40)**	Case series	Women treated for CSP at King's College Hospital, London between 1999-2005	36 years (range 27-43 years)	(Median) Vaginal birth=0; CS=2; Miscarriage=1; Ectopic=0; TOP=0	Not reported	TV USS	NR
Bignardi, 2010 **(n=7)**	Case series	Women treated for CSP at EPU, Nepan Hospital, Sydney between 2006-2008	34 years (range 23-41 years)	1 CS n= 6/7 2 CS n=1/7	Vaginal bleeding n=3/7; Vaginal bleeding + abdo pain n=1/7; Asymptomatic n= 3/7 Other: Following IVF= 2/7 Median GA= 44	TV USS Cardiac activity present y= 4/7	1563
Deans, 2010 **(n=6)**	Case series	Women diagnosed with CSP at Royal Hospital for Women, Sydney between 2004-2007	41 years (range 33-41 years)	Previous CS: 1 CS n= 4/6 2 CS n= 2/6	Median GA= 6.5 weeks	TV USS Cardiac activity y= 3/6	294
Halperin, 2009 **(n=6)**	Case series	Women diagnosed with CSP at Assaf Harofe Medical Centre, Tek-Aviv between 2004-2007	35 years (range 27-44 years)	2 previous CS n= 6/6	Median GA= 14weeks	TV and TA USS	Not reported
Ko, 2014	Case series	Women diagnosed with CSP at Queen Mary Hospital, China over a	34.1 years +/- 4.1 years	Previous CS 1 CS= 17/22	Vaginal bleeding n=19/22; abdo pain n=2/22	TV USS	28 943 IU/L (range 346 – 139 653)

(n=22)		10 year period (2004-2013)		2 CS= 5/22 Median interval CS to CSP = 2 years (range 6mths-11 years) Spontaneous preg n=19/22; ART n=3/22	Median GA= 6.7 weeks (range 4.7 – 11.8 weeks)	Heterogenous mass n=22/22; GS n=18/22; Cardiac activity n=12/22; Median myometrial thickness 1.5mm (range 1-8mm)	
Li, 2014 **(n=39)**	Case series	Women treated for CSP at Peking Union Medical College Hospital from 2005-2012	33 years +/- 5 years	Previous CS: 1 CS =not reported;2 CS= 5/39 Median interval from CS – CSP =4years	Vaginal bleeding n=35/39	TV USS: Cystic solid or solid mass with mixed echoes in the lower anterior uterine wall, surrounded by peritrophoblastic vasculature	
Michener, 2009 **(n=13)**	Case series	Cases of CSP seen at the King Edward Memorial Hospital, Australia	34 years (IQR 32.2, 35.2)	Median parity=2 (IQR 1,3) Previous CS: 1 CS= 9/13 2 CS= 2/13 3 CS= 1; 4 CS = 1 Median interval between CS and CSP = 2 years (IQR 1.75, 4.6)	Vaginal bleeding n=9/13 Median GA 6.8 weeks (range 5.5-11.5)	TV USS n=9/13 Cardiac activity n= 5/13	Median= 9035
Ong, 2014	Case series	All women diagnosed and treated for CSP at KK Women's and	30 years (range 21-34 years)	Previous CS: 1 CS= 2/5	Vaginal spotting= 2/5 Vaginal spotting+pain= 3/5	TV USS	Median= 1792.5

(n=5)		Children's Hospital, Singapore between 2012 and 2013		2 CS= 3/5			
Shi, 2014 **(n=57)**	Case series	All women undergoing treatment for CSP at Affiliated Hospital of Hebei University, China between 2011 and 2013	Not extractable	Not extractable	Not extractable	Not extractable	Not extractable
Tagore, 2010 **(n=6)**	Case series	Women managed for CSP at KK Women's and Children's Hospital, Singapore between 2004 - 2008	32.5 years (range 27-41 years)	Previous CS 1 CS= 3/6 2 CS= 3/6	Not reported	TV USS Cardiac activity n=2/6	8647.5
Uysal, 2013 **(n=7)**	Case series	Women managed for CSP at Konak Women's Health and Maternity Hospital, Turkey	28 years (range 22-41)	Previous C/S 1 CS=5/7 2 CS= 2/7 Interval between CS and CSP= 6mths-10 mths Previous CSP = 1/7	Amenorrhoea n=7/7	TV USS Cardiac activity= 3/7	5978
Yang, 2010 **(n=66)**	Case series	Women diagnosed with CSP at West China Second University Hospital of Sichuan University, China between 2003 and 2008	31.6 years (range 19-48 years)	Range 1-3 previous CS Median time from previous CS to CSP = 3.3years	Abdominal pain n= 28/66; Vaginal bleeding n=34/66	TV USS and Doppler	440-129520

NR= Not reported; TV USS= Transvaginal Ultrasound Scan; BhCG = Beta Beta-Human Chorionic Gonadotropin; GA= Gestational Age**;** D&C= Diltation and Curettage; KCL= Potassium chloride; MTX= Methotrexate; NR = Not reported; Post op= Postoperative; UAE= Uterine Artey Embolisation

Table 2.2 Characteristics of included studies of CSP showing treatment outcome

Author	Primary treatment	Treatment success	Complication and Follow-up	Future pregnancy
Ben Nagi, 2007 **(n=40)**	Surgical evacuation = 28/40; Medical management 9/40; Expectant management=3/40	Surgical=28/28 Medical= 6/9 Expectant=0/3 (emergency hysterectomy= 2; miscarriage at 17 weeks, n=1)	NR	F/U data available for 29/38; 24/29 attempted pregnancy, of which 21/24 conceived. 1/20 had recurrent CSP
Bignardi, 2010 **(n=7)**	TRS (transrectal guided) surgical evacuation n=5/7 MTX n=2/7	Surgical= 5/5 Medical n=1/2; 3rd dose of MTX failed, TRS-guided aspiration performed	Surgical n= 0/5 Medical n=1/2 – lap repair of persistent myometrial defect	NR
Deans, 2010 **(n=6)**	Hysteroscopy and resection n= 4/6; Medical n=1/6; combined n =1/6	Surgery n=4/4; medical n=1/1; combined 1/1	Surgical n=1/4 haemorrhage, ergometrine and foley catheter used; Medical n=1/1 pesistent pain and haematoma	Of those planning for pregnancy n=2/4

Halperin, 2009 **(n=6)**	Surgical, D+C n=4 Medical n=2; - UAE and MTX = 1 -MTX = 1	Surgery 4/4 Medical 0/2	Surgery= blood transfusions n=2; DIC n=1 Medical: Rupture n=1, pt required laparotomy and excision, had bladder injury. Heavy bleeding n=1, laparotomy and excision performed	NR
Ko, 2014 **(n=22)**	Expectant= 4; Medical =12, of which MTX=9, MTX+KCL=3 Surgical = 4, of which US guided suction evacuation n= 3, Laparotomy n=1 2 transferred to another centre- outcomes unknown	Expectant= 4/4 Medical =9/12 Surgical = 3/4	BhCG to normalise mean=10 weeks (range 2-20 weeks) Time to complete resolution = 4 months (range 1-15 months)	4/ (denominator NR)
Li, 2014 **(n=39)**	Medical n=3, all MTX. Surgical n= 35: D+C n=16; Lap excision n= 15; TA hysterectomy n=4	MTX= 2/3 D+C= 11/16 Lap excision =15/15 TAH= 4/4	Not reported	NR
Michener, 2009 **(n=13)**	Methotrexate n=8 Surgical n=5: Emergency hysterectomy n=1 Suction curettage n=2 Elective hysterectomy=2	Medical n=5/8 Surgical n=5/5	Medical= life threatening bleeding, required emergency hysterectomy and HDU care Pt who had Emergency hysterectomy at presentation required HDU care	4/?

Ong, 2014 **(n=5)**	Medical: Methotrexate = 3/5 Surgical: Suction curettage= 2/5	Medical= 0/3 Surgical= 2/2	Medical-2 required suction curettage, 1 needed lap adhesiolysis and repair of defect + suction curettage BhCG to normalise in wks: 4, 4, 3,6, 3	NR
Shi, 2014 **(n=57)**	Medical: Embolisation= 22 Surgical: D+C= 12 Laparotomy= 8 TV debridement= 15	Embolisation n=19/22 D+C= 12/12 Laparotomy= 7/8 Transvaginal debridement= 13/15	NR	NR
Tagore, 2010 **(n=6)**	Medical- MTX n =3/6 Surgical- hysterotomy n=1/6 Laparotomy and excision n=1/6 Laparoscopy and excision= 1/6	Medical= 3/3 Surgical= 2/3- subtotal hysterectomy for massive bleeding following attempted hysterotomy	Surgical= 1/3- subtotal hysterectomy for massive bleeding following attempted hysterotomy	
Uysal, 2013 **(n=7)**	Medical- MTX n= 2/7 Intrasac KCL n=1/7 Surgical- D&C 3/7 Laparotomy and excision n=1/7	Medical- 1/3 Surgical n=4/4	Medical- vaginal bleeding n=2, curettage performed n=2 Surgical- bleeding following hysterotomy; cervical cerclage suturing and bilateral hypogastric artery ligation performed	

Yang, 2010 **(n=66)**	Medical: Systemic MTX- n=17/66 Surgical: D&C n=11/66 Combined UAE+ local MTX n=38/66	Medical n= 9/17 Surgical n=3/11	Medical- massive haemorrhage n=7/17- 2 needed hysterectomy; 5 needed extra MTX or D&C for failed treatment D&C- severe haemorrhage n=8/11- 3 needed hysterectomy, 1 wedge resection of pregnancy;

D&C= Diltation and Curettage; KCL= Potassium chloride; MTX= Methotrexate; NR = Not reported; Post op= Postoperative; UAE= Uterine Artey Embolisation

Figure 10. Study selection process for systematic review of management of caesarean scar pregnancy

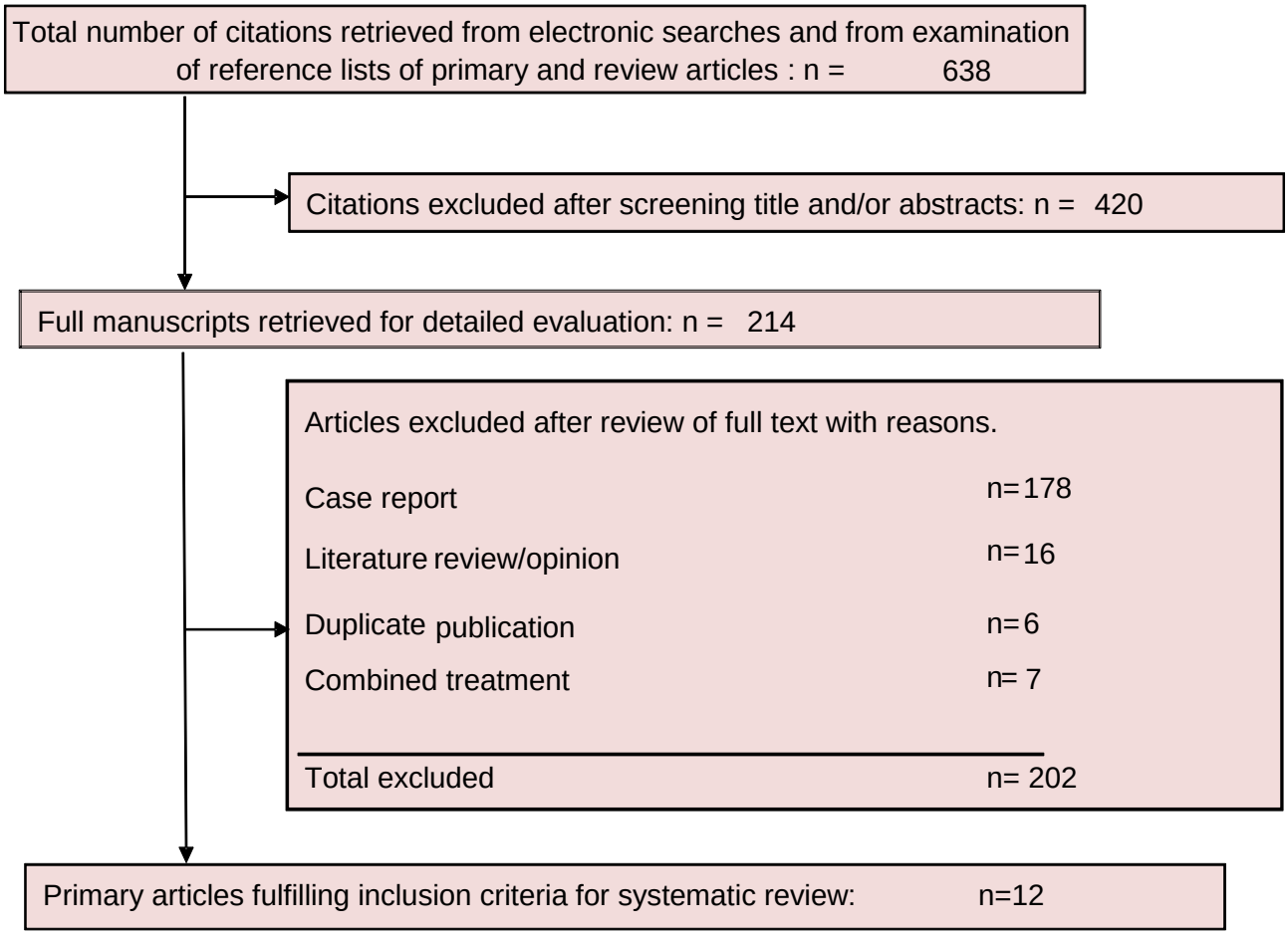


Table 3. Appraisal of methodological quality (Minors checklist) of included studies of CSP

	Ben Nagi 2007	Bignardi 2010	Deans 2010	Halperin 2009	Ko 2014	Li 2014	Michener 2009	Ong 2014	Shi 2014	Tagore 2010	Uysal 2013	Yang 2010
Aim	2	2	2	1	2	2	2	2	2	2	1	2
Inclusion of patients	2	2	2	1	1	2	2	1	2	2	1	2
Prospective data collection	0	0	0	0	0	0	0	0	0	0	0	0
Appropriate end points	1	1	1	2	2	1	1	2	1	2	2	1
Unbiased end point assessment	2	0	0	1	2	0	0	2	0	2	2	0
Appropriate follow up	1	1	1	1	2	1	1	2	1	2	2	1
Loss of follow up <5%	1	0	1	0	1	1	1	2	1	1	1	1
Prospective study size calculation	0	0	0	0	0	0	0	0	0	0	0	0
Adequate control group	0	0	0	0	0	0	0	0	0	0	0	0
Contemporary groups	0	0	0	0	0	0	0	0	0	0	0	0
Baseline equivalence	1	1	1	1	1	1	1	1	1	1	1	1
Statistical Analysis	1	0	0	0	0	0	0	0	0	0	0	0
Score	11	7	8	11	11	8	8	12	8	12	10	8

Primary outcome - Treatment success

Expectant management

Two studies reported expectant management for the treatment of caesarean scar pregnancy; one study compared outcome following expectant management with medical treatment. The other study compared expectant management with surgical treatment. It was therefore not possible to meta-analyse for this treatment approach.

Medical vs Surgical treatment

Pooling of results from 12 studies that compared medical treatment with surgical treatment as primary management for caesarean scar pregnancy showed no difference in treatment success (RR=0.85, 95% CI 0.70–1.04, *p*=0.12, Figure 11). The I^2 value was 12% indicating little variation among the studies (*p*=0.33).

Outcome according to intervention

Methotrexate vs Surgical evacuation

Pooling of results from 9 studies that compared methotrexate with surgical evacuation as primary management for caesarean scar pregnancy did not show a difference in successful treatment outcome (RR=0.78, 95% CI 0.55–1.02, *p*=0.07, Figure 12). The I^2 value was 0% indicating no variation among the studies (*p*=0.47).

Methotrexate vs laparatomy and excision

Pooling of results from 3 studies that compared methotrexate with laparotomy and excision as primary management of caesarean scar pregnancy did not show a

difference in successful treatment outcome (RR=0.90, 95% CI 0.51–1.59, *p*=0.71, Figure 13). The I^2 value was 0% indicating no variation among the studies (*p*=0.87).

Methotrexate vs laparascopy and excision

Pooling of results from 2 studies that compared methotrexate with laparoscopy and excision as primary management of caesarean scar pregnancy did not show a difference in successful treatment outcome (RR=0.73, 95% CI 0.41–1.32, *p*=0.30, Figure 14).

Methotrexate vs hysteroscopic resection

Only one study compared outcome following treatment with methotrexate and hysteroscopic resection as primary outcome and therefore could not be meta-analysed (Figure 15).

Figure 11. Meta-analysis of studies of caesarean scar pregnancy for the outcome of successful treatment following primary management

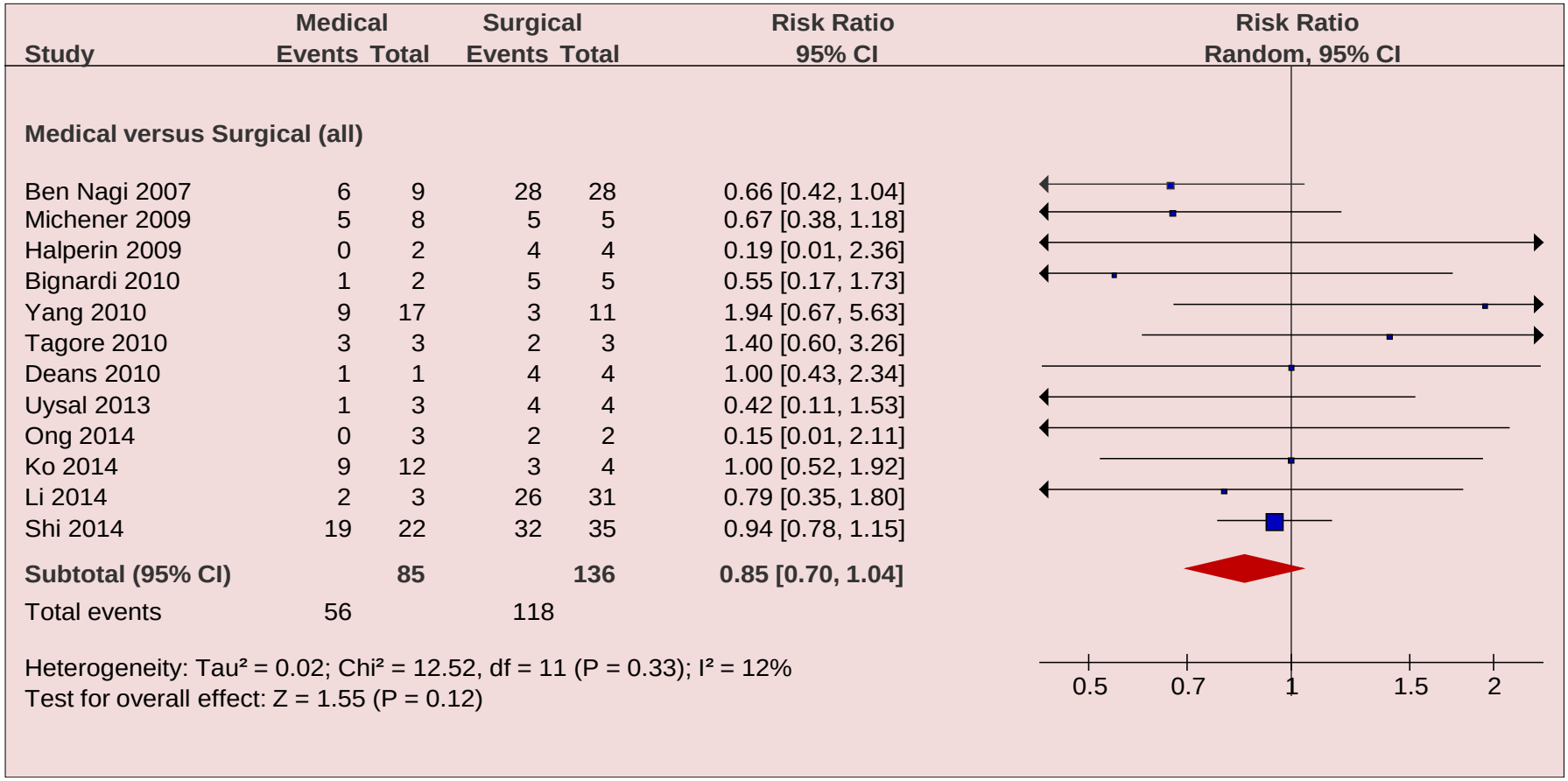


Figure 12. Meta-analysis of studies of caesarean scar pregnancy for the outcome of successful treatment: Methotrexate vs surgical evacuation

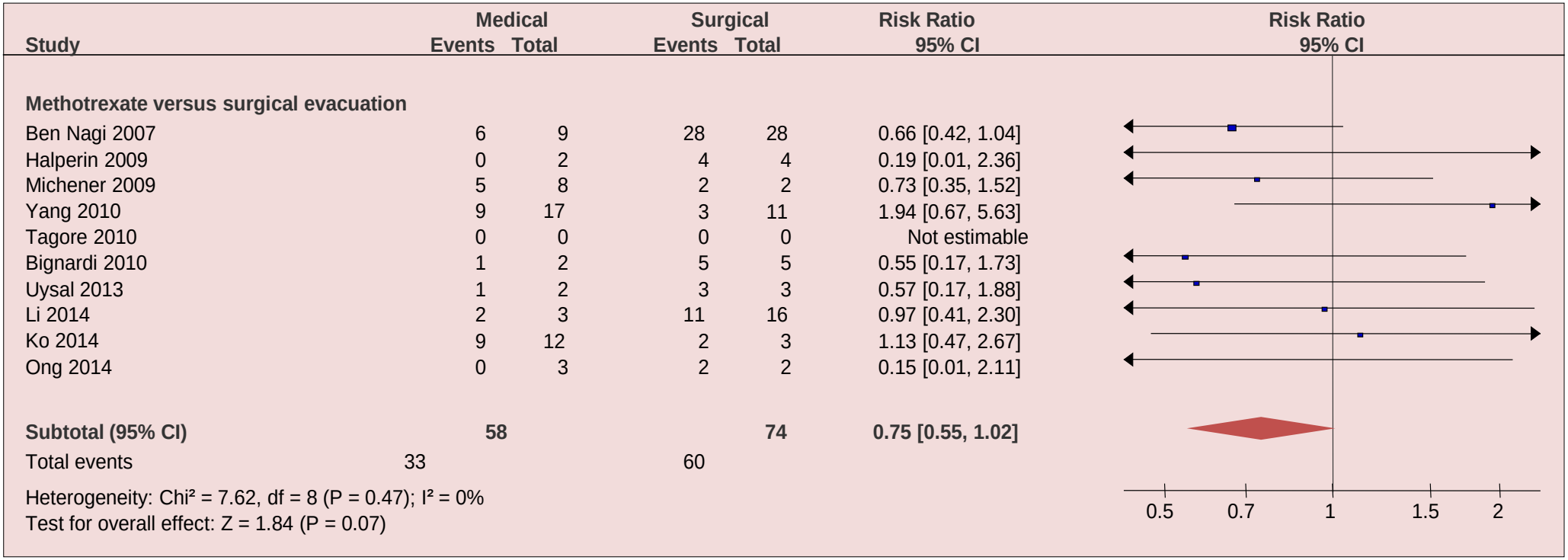


Figure 13. Meta-analysis of studies of caesarean scar pregnancy for the outcome of successful treatment: Methotrexate vs Laparotomy and excision

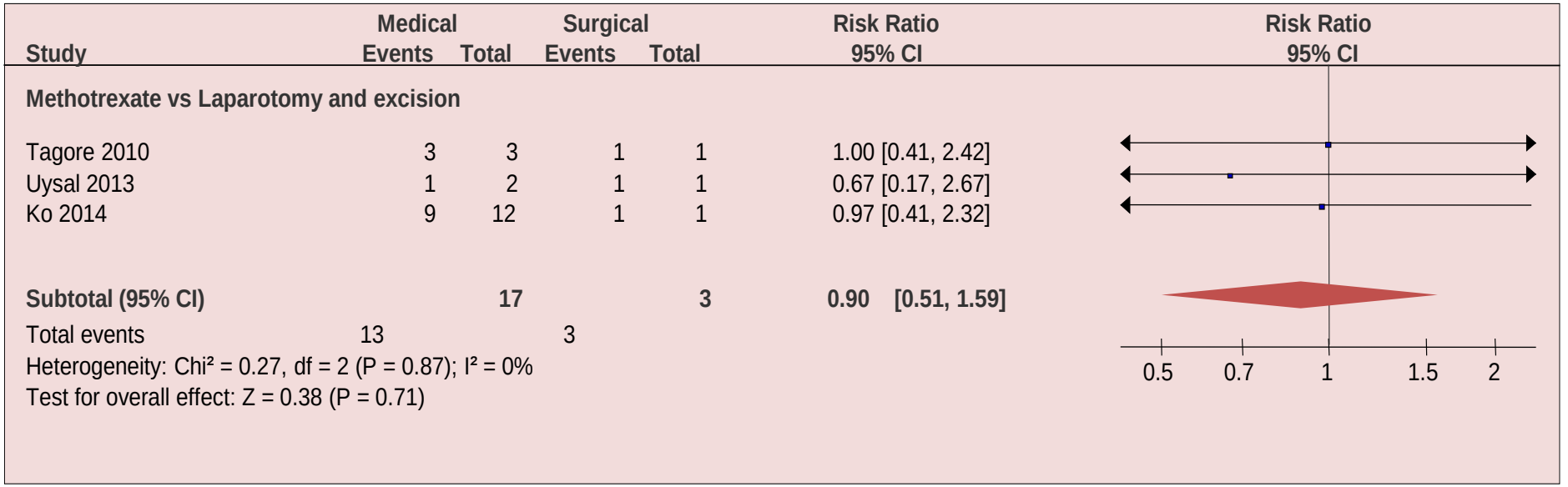
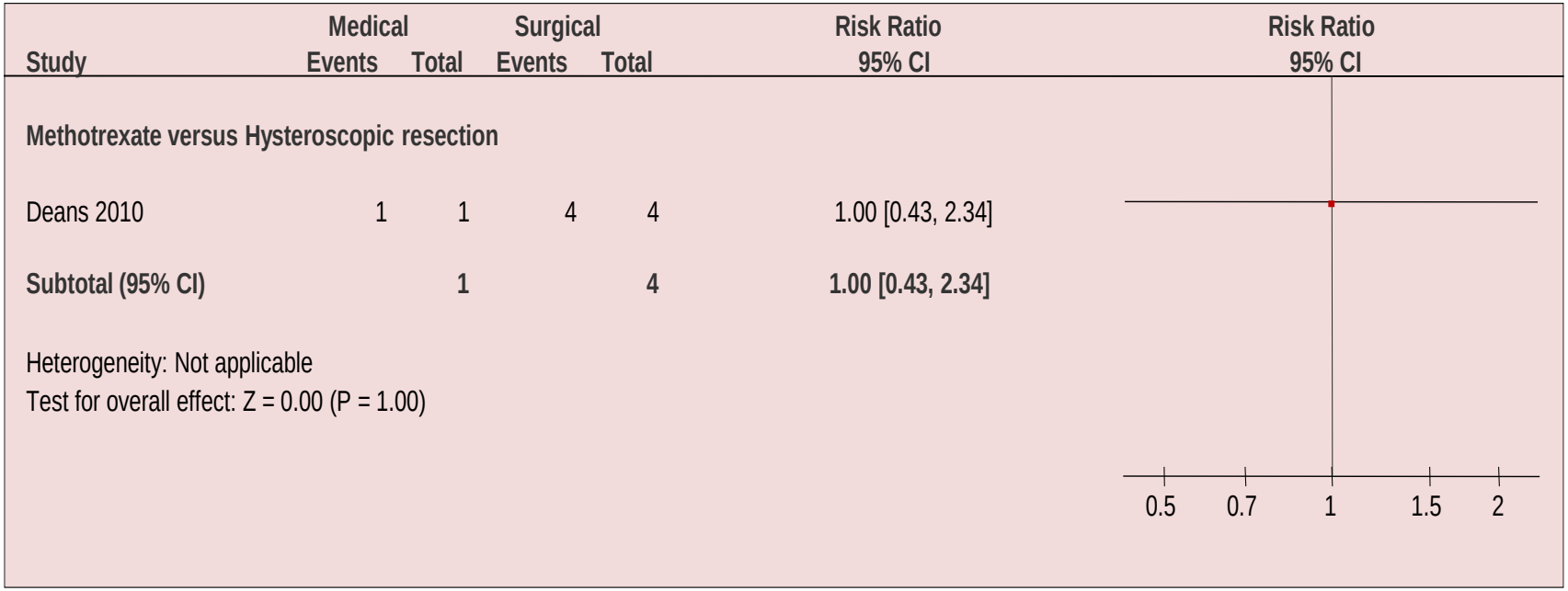


Figure 14. Meta-analysis of studies of caesarean scar pregnancy for the outcome of successful treatment: Methotrexate vs Laparoscopic excision

Figure 15. Meta-analysis of studies of caesarean scar pregnancy for the outcome of successful treatment: Methotrexate vs Hysteroscopic resection



Secondary outcomes

Need for secondary intervention

Pooling of results from 8 studies that reported the need for secondary intervention for caesarean scar pregnancy showed an increase in the secondary intervention rate in women treated with medical treatment when compared to those treated surgically (RR=2.50, 95% CI 1.10–5.65, *p*=0.03, Figure 16)). The I^2 value was 15% indicating little variation among the studies (*p*=0.31).

Complications

Pooling of results from 8 studies that compared medical and surgical treatment as primary management of caesarean scar pregnancy did not show a difference in complication rate (RR=1.24, 95% CI 0.67–2.29, *p*=0.50, Figure 17). The I^2 value was 19% indicating some variation among the studies (*p*=0.28).

Haemorrhage

Pooling of results from 6 studies that compared medical and surgical treatment as primary management of caesarean scar pregnancy did not show a difference in the risk of haemorrhage as a complication of treatment (RR=1.13, 95% CI 0.58–2.22, *p*=0.50). The I^2 value was 27% indicating some variation among the studies (*p*=0.28).

Persistent defect

Pooling of results from 2 studies that compared medical and surgical treatment as primary management of caesarean scar pregnancy did not show a difference in the risk of persistent myometrial defect necessitating repair as a complication of treatment (RR=3.64, 95% CI 0.48–27.43, p=0.21). The I^2 value was 0% indicating consistency among the studies (p=0.63).

Rupture

Only one study reported this outcome. This was a complication which occurred following medical treatment of caesarean scar pregnancy.

Hysterectomy

Pooling of results from 3 studies that compared medical and surgical treatment as primary management of caesarean scar pregnancy did not show a difference in the risk of hysterectomy as a complication of treatment (RR=0.57, 95% CI 0.17–1.93, p=0.37). The I^2 value was 0% indicating consistency among the studies (p=0.64).

Figure 16. Meta-analysis of studies of caesarean scar pregnancy for the outcome of need for additional interventions

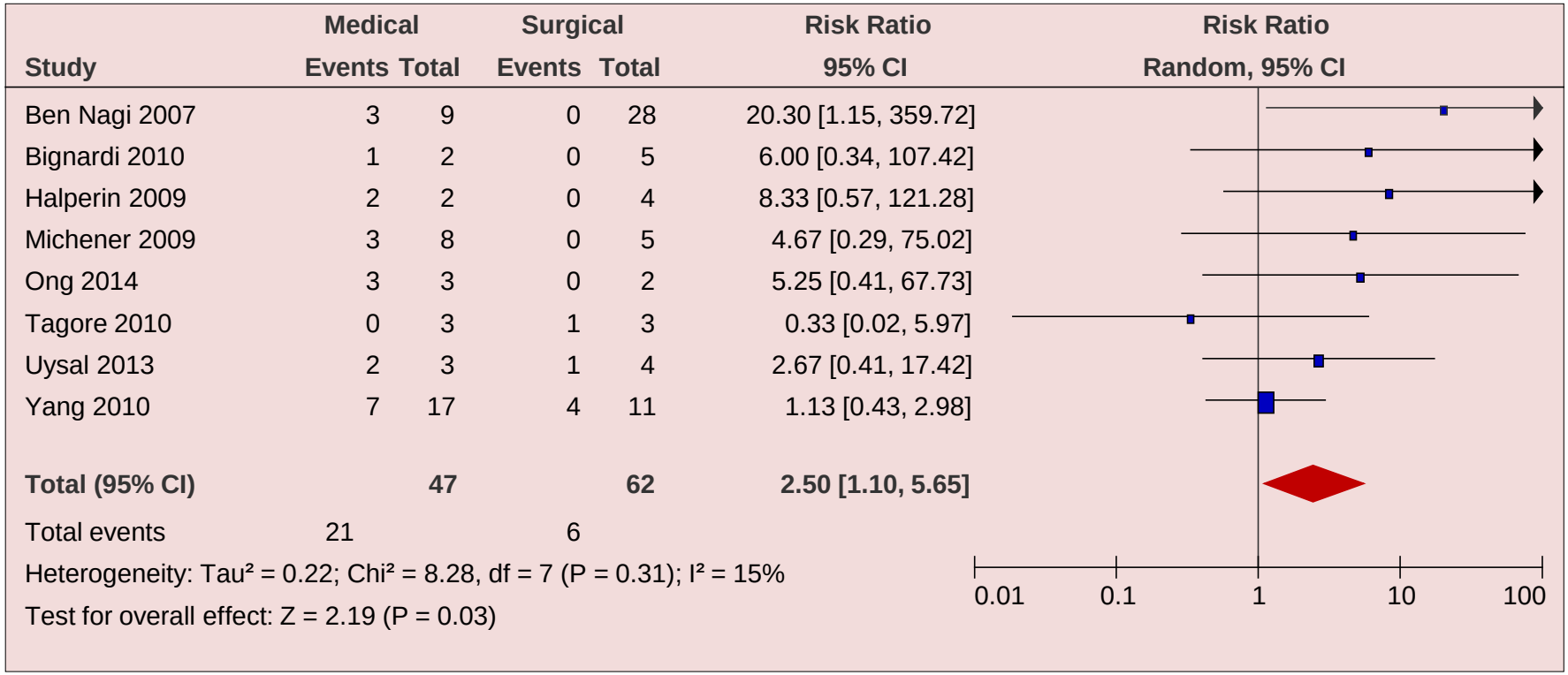
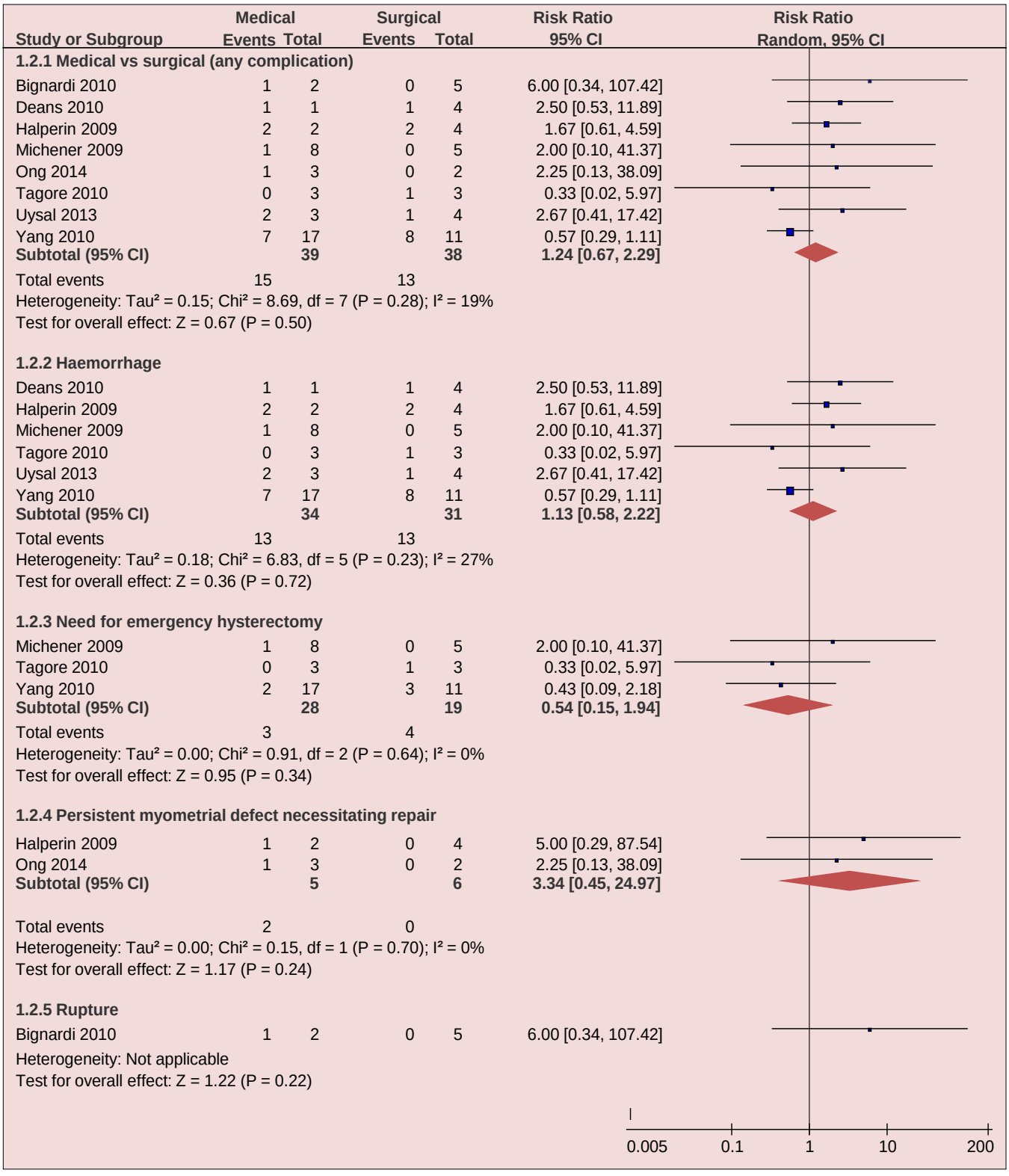


Figure 17. Meta-analysis of studies of caesarean scar pregnancy for the outcome of complications



DISCUSSION

This systematic review, which included 12 studies, found that medical and surgical treatment were equally as effective when used as primary management for caesarean scar pregnancy. However, additional intervention was required more often in women undergoing medical treatment when compared to those that had surgical treatment. No difference was found in the risk of complications, including haemorrhage, need for emergency hysterectomy, persistent myometrial defects requiring repair, and rupture.

There are several factors that give strength to the findings of this study. Firstly, I performed an extensive search strategy and used valid data synthesis methods. No language restrictions were placed on the search or included study.

The weaknesses in the study are mainly related to the quality of the included studies. 9 of the included studies were of observational study design and 3 were case series. While there are clear limitations to the methodology of case series, the observation of a series of patients can add to our understanding of aetiology, pathogenesis, natural history, and treatment, particularly in rare diseases.

A serious concern is the possibility of false positive cases being reported as caesarean scar pregnancies. All of the women in the included studies had transvaginal ultrasonography. There currently does not exist a validated ultrasound criteria for the diagnosis of CSP. Jurkovic (41) proposed the following criteria to aid

diagnosis: presence of gestational sac or placental tissue anteriorly at the level of the internal os, clear evidence of pregnancy invading into the myometrium, evidence of sustained peritrophoblastic circulation on colour Doppler examination, characterised by high blood-flow velocity (over 20cm/sec) and low impedance (PI<1) circulation, and negative sliding organ sign (inability to displace the gestational sac from its position using gentle pressure with a transvaginal probe). Whether this criteria is used widely in practice is unknown.

Magnetic Resonance Imaging (MRI) may be a useful adjunct to ultrasonography for the diagnosis of caesarean scar pregnancy.(56;57) MRI can provide additional information on the volume of the lesion and extent of myometrial involvement. (57) This information can potentially aid clinicians to assess the appropriateness of the management approach. For example, surgical management may be considered in women with significantly deficient myometrial scar. However, a major limitation of MRI is its long acquisition time and cost and may be better reserved for cases where TVS and colour flow doppler are inconclusive.

Two of the included case series as well as several published case reports have reported women who were treated conservatively after diagnosis of caesarean scar pregnancy. In two cases, close observation with twice weekly BhCG and USS scan monitoring showed a resolution of pregnancy on scan and BhCG within 2 months, with no complications or further treatment required. Two women are reported to have kept scar pregnancies till 35 weeks of gestation; one woman went into pre-term labour and required an emergency caesarean section, and the other was

admitted with severe abdominal pain. Both had healthy babies, but with the consequence of life threatening haemorrhage, resulting in disseminated intravascular coagulopathy with 16 units of blood transfused in one case, and both needed a hysterectomy. In the remaining 6 cases, a conservative approach was intended, however, salvage treatment was performed due to life threatening haemorrhage, or persistent gestational tissue on ultrasonography. One woman had severe haemorrhage and underwent an emergency laparotomy and total abdominal hysterectomy. Another woman had a dilatation and curettage for persistent gestational tissue which resulted in a massive bleed necessitating a laparotomy and hysterectomy for uncontrollable intra-operative bleeding. Due to persistent gestational tissue on scan and raised BhCG, two other women underwent surgical treatment; in one case, a laparoscopy was performed and was converted to a laparotomy, with excision of tissue and repair of the dehiscent scar. In the other, a laparoscopy was performed, and the pregnancy tissue was resected hysteroscopically.

In reported cases of heterotopic pregnancies, selective embryo reduction of a caesarean ectopic was shown to result in the delivery of a healthy infant, but often with consequences of pre-term labour, haemorrhage or premature rupture of membranes.

Given the quality of the included studies and concerns regarding reporting bias and the potential of false positive cases being reported, firm inferences cannot be drawn from the findings of this review. A nationwide collaboration to study this rare condition could enable higher quality prospective research to improve our

knowledge on best management of this condition, and to guide further research in this area.

CHAPTER 4:

CAESAREAN SCAR PREGNANCY SURVEILLANCE PROTOCOL

AIM

To use the UK Early Pregnancy Surveillance Service (UKEPSS) network to study caesarean scar Pregnancy.

OBJECTIVES

1. To establish the incidence of caesarean scar pregnancy
2. To identify the presenting features of caesarean scar pregnancy.
3. To identify the risk factors associated with this condition.
4. To evaluate additional diagnostic information gained from 3D Ultrasound, Doppler, MRI and CT over the reference standard of greyscale 2D ultrasonography.
5. To explore the variations in management and outcomes for this condition.

BACKGROUND

In this condition the pregnancy is partially or completely surrounded by myometrium and fibrous tissue of the scar of the prior lower uterine segment. It is estimated to occur in 0.15% of women with a history of at least one caesarean delivery. (19) Audit from a large tertiary unit (University College London) showed an incidence of 1:400 (0.25%) after one caesraean section and 1:50 (2%) after two or more Caesarean deliveries. The number of published case reports has increased over recent years, possibly reflecting the rising number of caesareans being performed or the more widespread use of transvaginal ultrasonography.

CLINICAL DILEMMAS: WHY A STUDY IS NEEDED

Diagnosis

Differentiating between spontaneous miscarriage, cervical pregnancy and caesarean scar pregnancy can be difficult. The majority of caesarean scar pregnancies fail spontaneously early in the first trimester. In the minority of cases a live foetus develops and the pregnancy could progress beyond the first trimester. In these cases a delay in diagnosis and treatment can lead to life threatening haemorrhage, hysterectomy or rupture of the uterus.(19;58;59) Early diagnosis is considered effective at reducing these risks. Through this study, we will study the application of the existing ultrasound diagnostic criteria and assess the role of 3D ultrasound scanning and 3D Power Doppler in providing additional diagnostic information. Furthermore, the use of magnetic resonance imaging (MRI) as an adjunct will be examined.

Risk factors

The risk of recurrence and the effect of interval between the previous caesarean delivery and a caesarean scar pregnancy is currently unknown. An increased risk has been reported in women having caesarean breech deliveries. (58) Potential predisposing factors such as a history of dilatation and curettage, placental pathology, ectopic pregnancy, uterine closure and IVF require further investigation. This information will aid early detection and counselling for women at risk.

Management

There is currently no agreement on the management for caesarean scar pregnancies. Delivery of a live term baby following expectant management has been reported in a few cases but with severe consequences to the mother. For this study we intend to compare expectant, medical and surgical management, investigating outcomes in terms of resolution of pregnancy, complications and length of follow up. Specifically, we will explore the effect of treatment with methotrexate, comparing systemic administration with local injection. Outcomes of different surgical techniques, including laparotomy with wedge resection, operative laparoscopy, and hysteroscopic approaches will be compared. Furthermore, combined medical and surgical treatment (such as local injection of methotrexate with transcervical aspiration of the pregnancy) will be studied. The use of selective uterine artery embolisation also requires further assessment. This information will be used to develop follow-up protocols and guidelines on management.

RESEARCH QUESTIONS AND DESIGNS

Using the UK Early Pregnancy Surveillance Service to identify cases of caesarean

scar pregnancy the following non-interventional descriptive studies will be conducted:

1) **Case-control study:** the aim is to identify risk factors for caesarean scar pregnancy, with a particular focus on modifiable risk factors. For instance, is the method of uterine closure (with single or double layer suturing) associated with caesarean scar pregnancy? Is the number of previous caesarean sections associated with caesarean scar pregnancy? Is BMI associated with caesarean scar pregnancy? The control group will consist of women who have a history of at least one previous caesarean section, but no caesarean scar pregnancy. For each case of caesarean scar pregnancy reported, two controls will be sought from the reporting hospital.

2) **Study of additional information gained from added tests:** The standard method for diagnosis is ultrasound; in this study we will evaluate the additional test information gained from three-dimensional ultrasonography, magnetic resonance imaging and computer tomography (CT) scanning.

3) **Cohort study:** Treatment methods and outcomes will be gathered and reported. Expectant, medical and/or surgical treatment is possible, and we will report outcomes by different treatment methods, and subgroups of patients.

5. CASE IDENTIFICATION

Cases will be identified through the monthly mailing of the UK Early Pregnancy Surveillance Service, comprising of early pregnancy units, acute gynaecology and

obstetric units. The cases will be women in the UK diagnosed as having a caesarean scar pregnancy. Given the recognised variability in ultrasound experience as well as the lack of a universally agreed diagnostic criteria, the UKEPSS study steering committee has adopted the sonographic criteria developed by Jurkovic et al (Figure 18), which will be distributed to all participating units, as a guide to objectively assess whether submitted cases are true cases of caesarean scar pregnancy. It is possible that units may have a different criteria for diagnosis and the CRF has been left open to allow centres to report other scan findings which may aid in the diagnosis of this condition. Therefore the proposed criteria is a guide but is not definitive. Centres will also be encouraged to submit anonymised ultrasound images for assessment by the study steering committee.

Figure 18. Sonographic criteria for the diagnosis of caesarean scar pregnancy

Ultrasound diagnostic criteria

- Presence of gestational sac or placental tissue anteriorly at the level of the internal os
- Clear evidence of pregnancy invading into the myometrium
- Evidence of sustained peritrophoblastic circulation on colour Doppler examination, characterised by high blood-flow velocity (over 20cm/sec) and low impedance (PI<1) circulation
- Negative sliding organ sign (inability to displace the gestational sac from its position using gentle pressure with a transvaginal probe)

Based on criteria developed by Jurkovic et al. and adopted by the UKEPSS Study Management Group for the purpose of this study.

SONOGRAPHIC IMAGES OF CSP (*Images (19-24) included and used with permission from Mr Davor Jurkovic, FRCOG, University College London)*

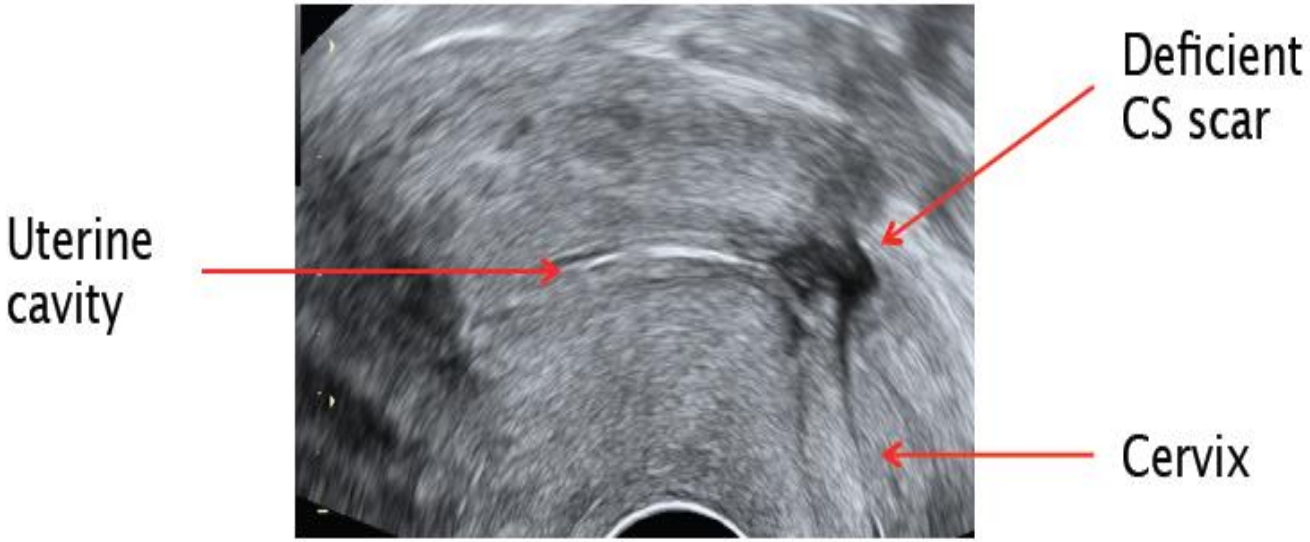


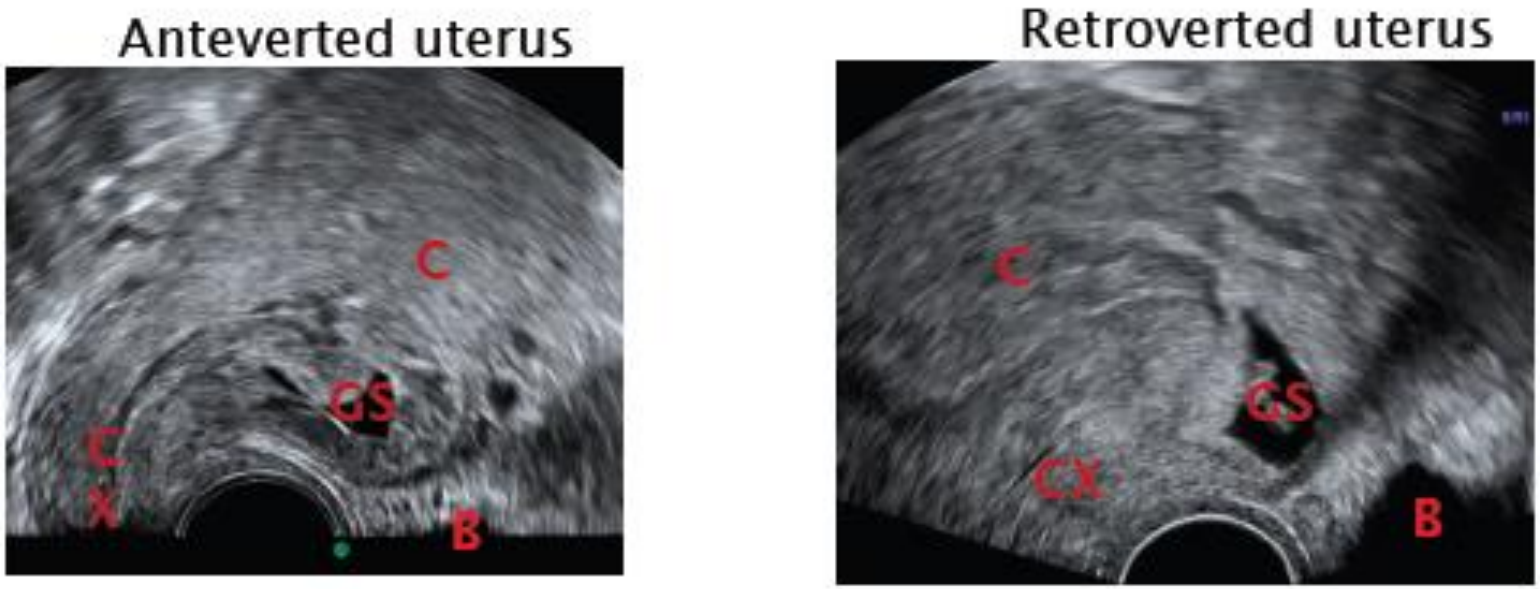
Figure 19: Gestational sac implantation in deficient CS scar

Why does a scar pregnancy occur?

The gestational sac implants into a deficient lower segment uterine caesarean section scar.

There is a lack of decidua at the level of scar which facilitates trophoblast invasion into the myometrium and development of abnormally adherent placenta

Figure 20: Implantation into the anterior uterine wall (transducer bottom of the image)



C – uterine cavity, CX – cervix, B- urinary bladder, GS – gestational sac)

Take a note of uterine version/flexion in order to correctly identify anterior and uterine walls.

Pregnancy located outside the uterine cavity (C) and extending beyond endometrial-myometrial junction at or below the level of the internal os

Figure 21: Pregnancy outside of the uterine cavity

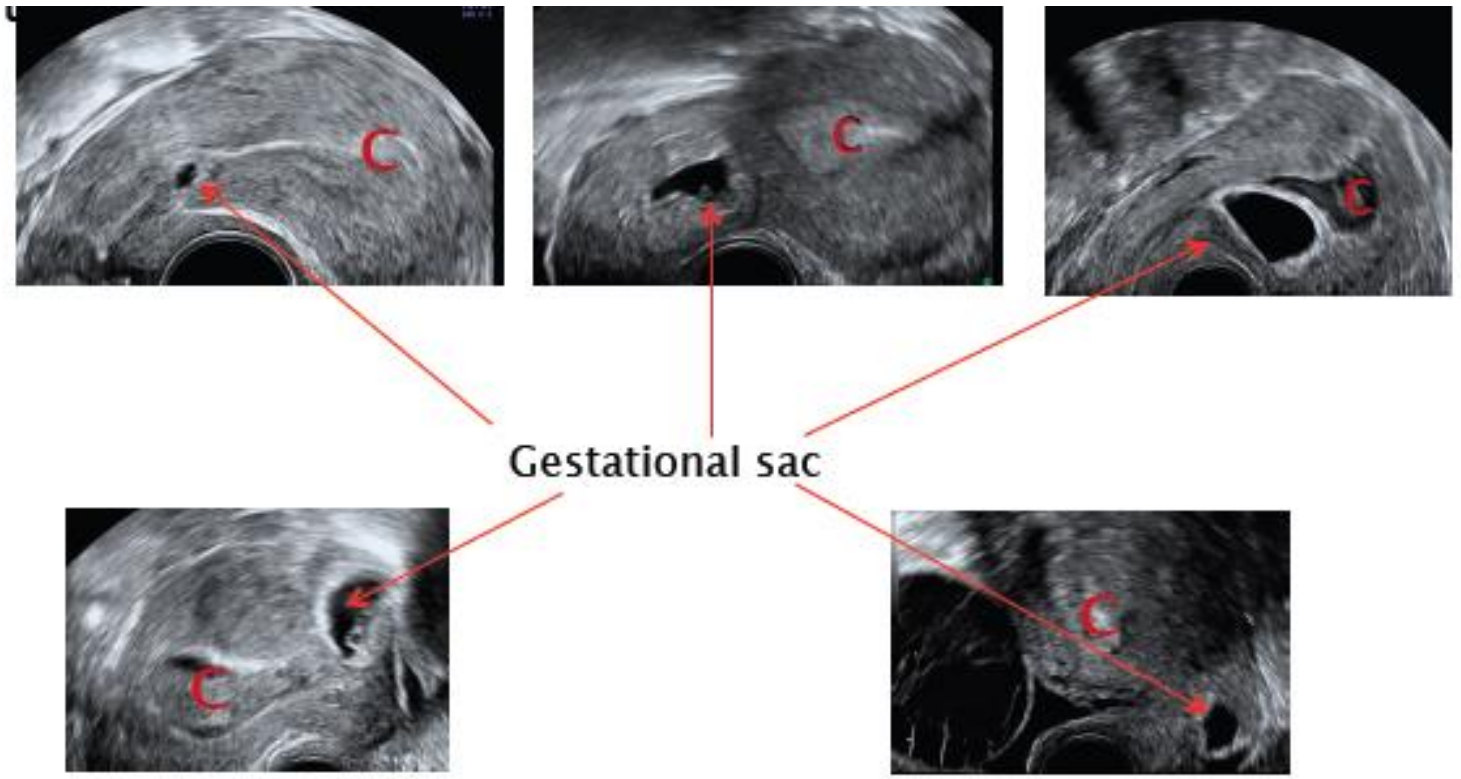
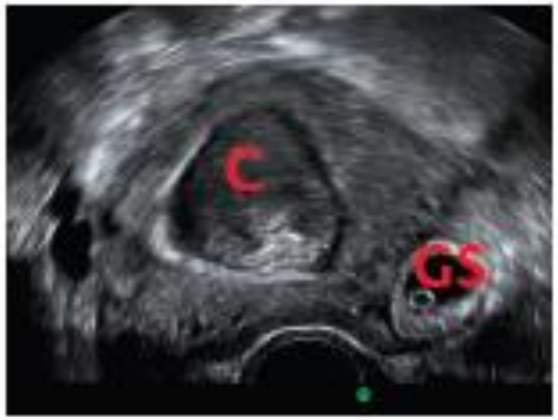
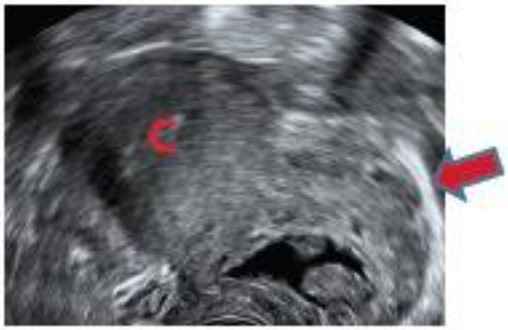


Figure 22: Myometrial involvement

Gestational sac (GS) outside the uterine cavity (C) completely embedded into the myometrium



Anterior herniation towards the bladder (arrow) confirms thediagnosis of myometrial implantation



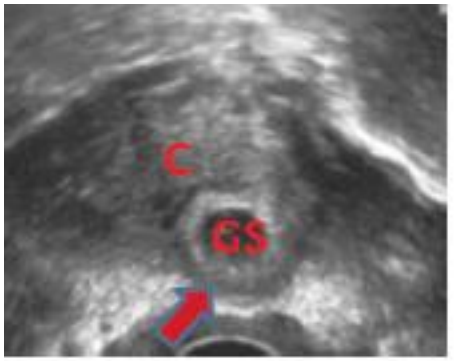


Figure 23: Peri-trophoblastic flow

Colour Doppler demonstrates high vascularity adjacent to the anterior aspect of the gestational sac (GS), uterine cavity (C)

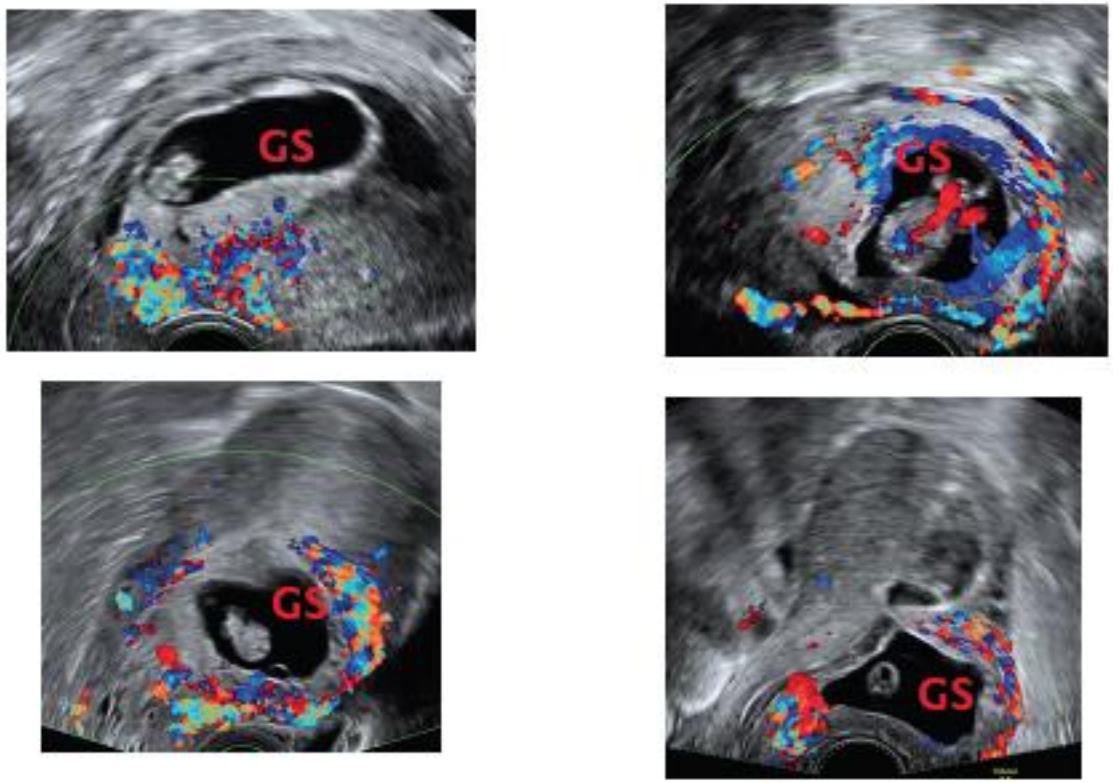


Figure 24: Using Doppler to avoid false positive diagnosis

• Gestational sac overlying the scar (arrow), but Doppler shows posterior implantation away from the scar

• Gestational sac overlying the scar (arrow) but blood supply indicates implantation inside the uterine cavity which is suggestive of uncomplicatedmiscarriage

• Inevitable miscarriage – although the cardiac action is still maintained the lack of peri-trophoblastic flow and high cord insertion (arrow) are suggestive of cervical phase of miscarriage

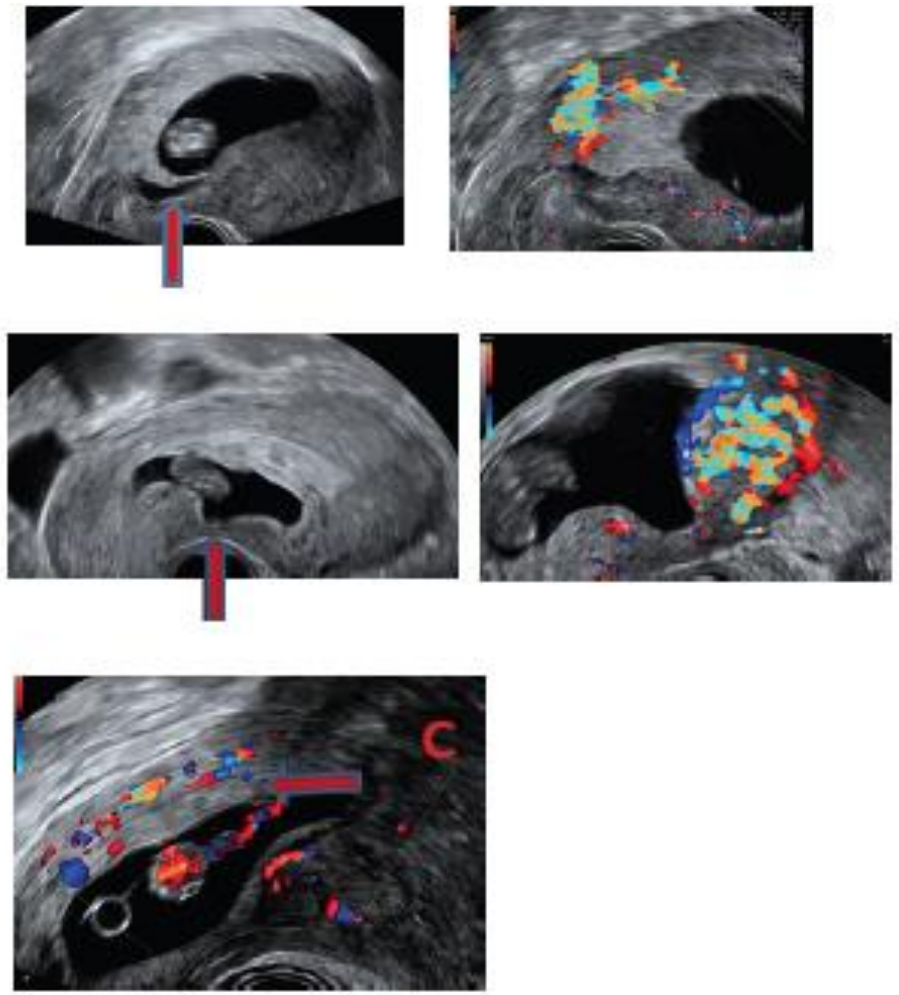
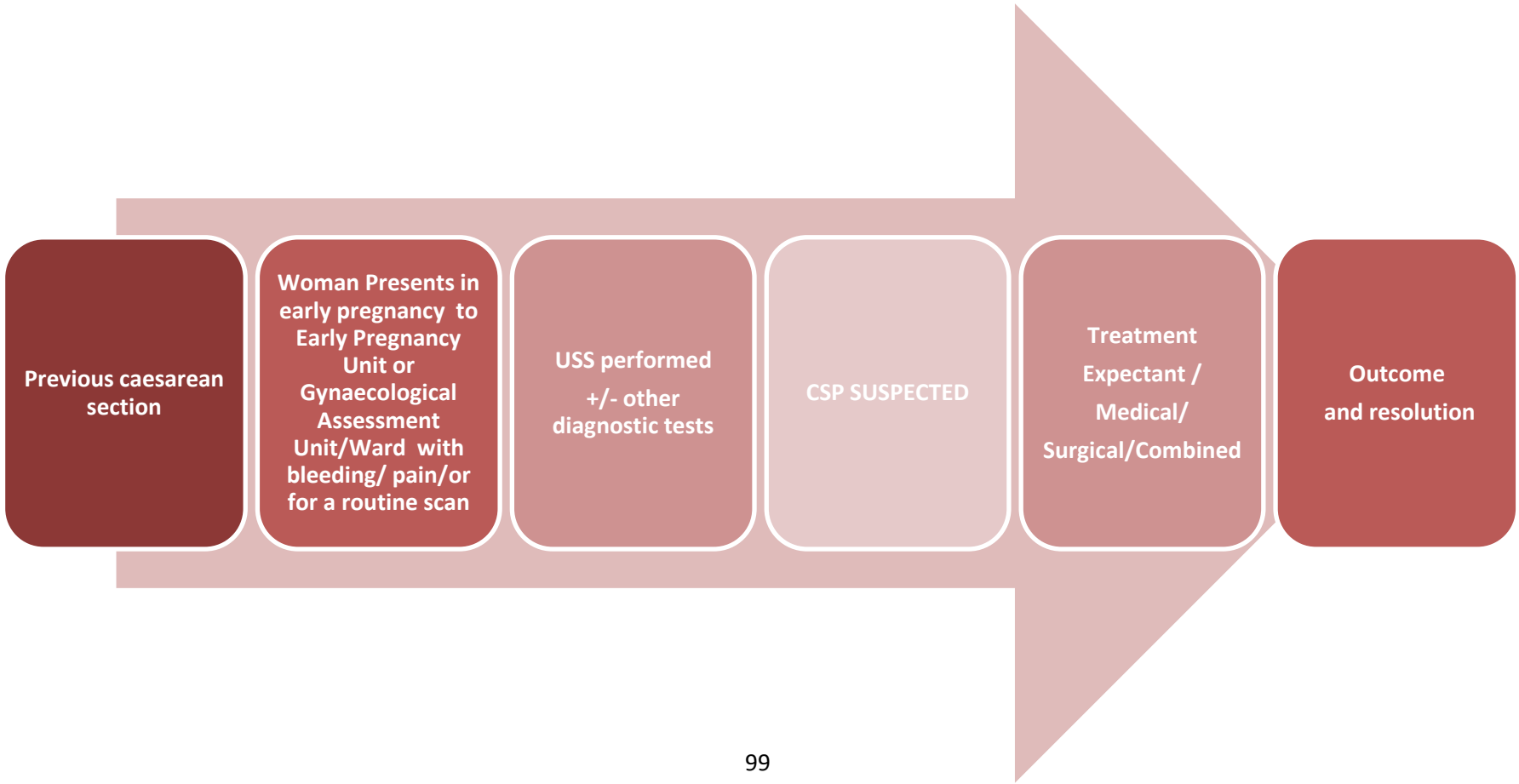


Figure 25. Expected care pathway for women presenting with caesarean scar pregnancy



CONTROL IDENTIFICATION

Controls will be women with a history of at least one previous caesarean section delivery, of approximately the same gestation as the case, diagnosed with an intrauterine pregnancy on early pregnancy scan (i.e not a CSP, seen for other symptoms). The clinician reporting each case will be asked to supply data for two control women seen at their unit.

DATA GATHERING

Monthly electronic cards and case reporting forms will be sent to nominated reporting clinicians to collect anonymised information using a secure electronic data capture system. The case report form will seek to confirm that the reported case meets the case definition and will collect information on each woman's presenting features, risk factors, diagnosis, management and outcomes. No personally identifiable information, such as names, date of birth, addresses, or hospital numbers will be collected by UKEPSS. All information sought will be anonymous and will be completed by the clinical team from the woman's case notes, without requiring reference to any other sources of information. Each unit will be advised to keep a centre specific case ID number for each case reported, such that if further information is needed the relevant data can be sought. The study thus involves provision of information only. The woman's management will not be changed in any way by inclusion of her data in the study, and patients will not be contacted directly at any point either by the central research team or by local collaborating clinicians.

CONSENT

This is a non-interventional (descriptive) study only. The study seeks to describe the disease and will collect information only. The central team will not seek to collect any names, addresses, dates of birth, hospital or NHS numbers in order that none of the participants are individually identifiable. Patients will be managed by their usual clinical team and will receive the usual management for their care at hospital. Information will be collected from the clinical team responsible for each patient after the initial diagnosis. The management of each woman participating will not be altered in any way by participation in the study. The anonymous information will be used to calculate incidence rates, and to study variation in management and outcome, to further improve patient care.

STUDY SIZE

We will study all cases gathered in one year from the start of surveillance (February 2014). In 2008, 147 726 caesarean section (C/S) deliveries were performed. Based on the reported incidence of caesarean scar pregnancy of 0.15%, data on approximately 225 cases could be collected over a one year surveillance period.

DATA STORAGE

Anonymised data will be acquired and stored on a secure online Electronic Data Capture (EDC) system that will be developed and delivered to ISO 9001:2000 standards and in compliance with FDA CRF21:11 requirements. The system will be designed, developed and maintained by MedSciNet, based at King's College

University (London), who have over 10 years' experience in supporting 38 clinical trials, 17 registries, and 9 resource centres, including international databases for WHO.

STATISTICAL ANALYSIS

For descriptive studies, we will report frequencies and proportions with confidence intervals. For test performance, we will report additional cases identified by other tests, and the extra information they provided. For studies examining associations between various factors and successful outcome, we will report crude and adjusted odds ratios.

RESEARCH ETHICS COMMITTEE APPROVAL

This study has been approved by the North Wales REC (Central & East) (REC reference 13/WA/0318).

PROJECT MANAGEMENT

Day-to-day management of the project will be carried out by me. The overall conduct of the study will be monitored by the Steering Committee of the UK Early Pregnancy Surveillance System. Beyond this study, applications will be invited from clinicians and researchers for inclusion of suitable studies into the surveillance system. These will be considered by the UKEPSS steering committee. Potential studies will be lead by the applicants with the support of the UKEPSS steering committee, and will be considered against the following criteria:

1- The condition is an important cause of maternal morbidity and/or mortality.

2- The condition is an uncommon disorder of pregnancy, thus inclusion within the study programme of UKEPSS will not impose too great a burden on reporting clinicians (usually no more than one case per 2000 pregnancies

annually in the UK).

3- The research questions posed by the study can be suitably addressed using the UKEPSS methodology (prospective descriptive, cohort or case–control studies).

4- Other sources of information exist to enhance and/or assess completeness of data collection.

DISSEMINATION AND PUBLICATION

UKEPSS has been proposed to address important clinical and public health issues concerning serious disorders of early pregnancy. The key aim of UKEPSS is to provide information which can be used to improve prevention, diagnosis, treatment and service planning for the NHS and policy makers. Furthermore, it will be important to feedback the outcomes of the study to the clinicians who participated in providing information. We will achieve this through a comprehensive dissemination strategy:

Guidelines: The information is expected to be rapidly incorporated into guidelines by AEPU, RCOG and NICE, and disseminated to Early Pregnancy Units for implementation.

Patient information resources: Production of lay information with links to appropriate patient support groups, including Miscarriage Association and Ectopic Pregnancy Trust.

Conferences: Patients and patient representative groups regularly attend the Association of Early Pregnancy Units (AEPU) conferences. Results will be presented annually at the AEPU conferences and at other appropriate conferences.

Key Research Findings Memos: These memos will be distributed to all reporting clinicians, steering committee members, Directors of Public Health in Strategic Health Authorities and Health Boards, Chief Medical Officers, Voluntary Groups in the early pregnancy field, the UK Department of Health, and the Patient Safety Observatory.

Newsletters: Quarterly newsletters on the progress of UKEPSS studies will be published and widely distributed to all stakeholders, including all participating UKEPSS units, the Association of Early Pregnancy Units, the Royal College of Obstetricians and Gynaecologist, the Early Pregnancy Clinical Studies Group, the Miscarriage Association. the Ectopic Pregnancy Trust and the Scottish Early Pregnancy Network.

Annual Report: This report will outline the studies undertaken during the preceding year and will provide a summary of the key outcomes. It will be widely distributed to all stakeholders.

Peer reviewed publications: Study investigators will give an undertaking to submit full results for publication in a peer-reviewed journal within 1 year of the completion of data collection. References to all completed studies will be listed both in the annual report and on the UKEPSS Website. We will disseminate completed papers to the Department of Health, the Scientific Advisory Committees of the Royal College of Obstetricians and Gynaecologists (RCOG), the Royal College of Nurses (RCN) and the Association of Early Pregnancy Units.

Teaching and training material: We will produce these for EPU clinicians, nurses, sonographers and trainees.

Media: Where the Steering Committee judges it appropriate, in consultation with the investigators and appropriate journal, a press release may be made to the media upon publication of particularly notable results.

UKEPSS Website: UKEPSS already has an active website (www.ukepss.org) which will become an important instrument for dissemination.

Data for systematic reviews and meta-analysis: The Study Steering Committee will aim to release data for synthesis by external researchers with a credible protocol.

CHAPTER 5

CAESAREAN SCAR PREGNANCY IN THE UK: INCIDENCE AND MANAGEMENT OUTCOMES. A NATIONAL, PROSPECTIVE, COHORT STUDY

ABSTRACT

Objective

To estimate the incidence of caesarean scar pregnancy (CSP) in the UK and to describe the outcomes for women according to treatment approach

Design

A national prospective cohort study using the UK Early Pregnancy Surveillance Service (UKEPSS)

Setting

Eighty six UK early pregnancy and gynaecology units

Population

Sixty women diagnosed with caesarean scar pregnancy between February 2014 and February 2015, and 211 comparison women who have previously had at least one caesarean section and who have an intrauterine pregnancy

Methods

Prospective cohort identification through the UKEPSS monthly mailing system

Main outcome measures

Incidence, success rates, complications. Unadjusted (OR) and adjusted (aOR) odds ratio estimates.

Results

The estimated UK incidence of CSP was 1 per 10 000 maternities [95% confidence interval (CI), 0.71 – 1.19]. Age, smoking, parity and number of caesarean sections were strongly associated with a risk of having a caesarean scar pregnancy. The mean age at presentation was 35 years (±4.8). The most common symptom at presentation was vaginal bleeding (46%) and the mean gestational age at presentation was 9 weeks (range 6-18 weeks). Transvaginal ultrasound scan was used as first line diagnostic tool in all cases where mode of investigation was reported (44/44, 100%). Expectant treatment was associated with the highest failure rate (66%) when compared with medical (53%) and surgical treatment (7%). 50% of women having medical management needed further intervention. Surgical treatment with dilatation and curettage was the most commonly used treatment approach, and was associated with the highest rate of successful treatment (93%) following primary management. Expectant management had the highest complication rate (50%) when compared with medical (37.5%) and surgical (37.9%) management.

Conclusion

Surgical management appears to be the most effective treatment approach, and is associated with less need for additional intervention and early discharge from care.

INTRODUCTION

A caesarean scar pregnancy is an ectopic pregnancy which is partially or completely surrounded by myometrium and fibrous tissue of the scar of the prior lower uterine segment. It is estimated to occur in 0.15% of women with a history of at least one caesarean delivery. (17) The number of reported cases has increased over recent years, possibly reflecting the rising number of caesareans performed and the more widespread use of transvaginal ultrasonography.

There is currently no agreement on the management for caesarean scar pregnancies. There are three main management approaches; expectant, medical and surgical treatment. Women are counselled about the management options and are given the choice to either continue with their pregnancy, to watch and wait or to terminate the pregnancy.

No population-wide prospective incidence studies of caesarean scar pregnancy have been undertaken previously and the UK incidence is unknown.

The aim of this study was to use the UK Early Pregnancy Surveillance Service to identify all women in the UK diagnosed with caesarean scar pregnancy. This study describes the reported cases, management and outcomes for both women and babies, and draws comparison with women delivering in the same units who have had an intrauterine pregnancy following previous caesarean section delivery.

METHODS

This was a national prospective cohort study. The cohort was defined as all women in the UK diagnosed with caesarean scar pregnancy between February 2014 and February 2015. For all women in the study, baseline data were recorded for age, ethnic background, smoking status at presentation, history of medical problems, parity, and caesarean section history. Moreover details on presentation with CSP, ultrasound scan findings, additional investigations, management approach, outcomes, complication and follow up duration was collected. The primary outcome of the study was to identify the incidence of caesarean scar pregnancy. The secondary outcome was successful treatment following primary management. Success was defined as completed treatment without the need for additional interventions. Other outcomes included time to discharge and complications according to management approach. Furthermore, the clinician reporting each case of CSP was asked to supply data for at least two controls, obtained from the same units and defined as women with an intrauterine pregnancy who have undergone at least one previous caesarean section. This was to enable the identification of predictive factors for developing a caesarean scar pregnancy, The UKEPSS general methodology and this study were approved by the North Wales Research Ethics Committee (REC reference 13/WA/0318).

Data collection

Cases were identified on a national basis through the monthly mailing of UKEPSS between February 2014 and February 2015. Clinicians were asked to report any woman diagnosed with caesarean scar pregnancy. The UKEPSS methodology has

been described in Chapter 2. In brief, every month UKEPSS electronic case notification cards were sent to nominated reporting clinicians in each hospital in the UK with a consultant-led early pregnancy unit, with a simple box to indicate whether they had seen a woman with CSP. They were also asked to return cards indicating a ‘‘nil report‘‘, in order that we could monitor card return rates and confirm the denominator to calculate the incidence rate. When a clinician returned a card indicating a case, they were then asked to complete an online data collection form asking for details of disease presentation, management and outcomes. All data collected were anonymous. Up to five reminders were sent if forms were incomplete.

Additional case ascertainment

To ensure all cases were identified, we independently contacted all early pregnancy and radiology departments, who were asked to report any cases of CSP, reporting only their year of birth and date of diagnosis. Where a case was identified which had apparently not been reported through UKEPSS, the relevant reporting clinician was contacted and asked to complete a data collection form. No additional new cases were identified through these three other sources.

Statistical analyses

Statistical analysis was carried out according to a pre-specified study protocol. I calculated incidence with 95% confidence intervals by using denominator data from the most recently available birth registration data as a proxy for the period between February 2013 and February 2014. Odds ratios (ORs) and adjusted odds ratios (aORs) with 95% confidence intervals (CI) were estimated for outcomes using logistic

regression. Survival analysis for time interval from presentation with caesarean scar pregnancy to resolution of CSP was performed using the Cox proportional hazards model. Survival was calculated for the cases according to treatment group using Kaplan-Meier estimates. (60;61) For the analysis of predictive variables, I used the Mann-Whitney *U* tests.

RESULTS

86 hospitals with consultant-led early pregnancy units (EPAU) maternity units contributed data to UKEPSS during the study period with 85% participation. Data collection was complete for 48/60 (80%) of cases. Additional reports were received from 3 (4%) radiology departments, although no new cases were identified through this source.

Sixty cases of caesarean scar pregnancy were reported through UKEPSS in a reported 646, 904 maternities, giving an incidence of 1 per 10 000 maternities (95% CI, 0.71 – 1.19).

Demographics

Table 4 shows the characteristics of women diagnosed with CSP and provides a comparison with controls. Univariate analysis of baseline characteristics in women with and without caesarean scar pregnancy showed that age, number of previous live births, smoking and previous number of caesarean section are associated with an increased risk of developing a caesarean scar pregnancy. No difference was noted in

ethnicity, previous uterine surgery (surgical termination of pregnancy and surgical management of miscarriage), and medical history.

Table 4. Univariate analysis for prediction of caesarean scar pregnancy in women who have had at least one previous caesarean section

Prognostic variable	Cases	Controls	Odds ratio (95% CI)	*P*
Age in years	N=(45)	N=70	2.02	0.04
< 35	21 (47%)	22 (31%)	(1.05- 3.86)	
> 35	24 (53%)	48 (69%)		
Parity*	N=48	N=70	3.42	0.03
1	16 (33%)	98 (50%)	(1.39 – 8.4)	
2	15 (32%)	64 (33%)		
≥3	17 (35%)	33 (17%)		
Ethnicity	N=60	N=70	0.96	0.06
White	45 (75%)	39 (56%)	(0.34 – 2.99)	
Black	2 (3%)	70 (10%)		
Asian	9 (15%)	20 (29%)		
Chinese	3 (5%)	1 (1%)		
Mixed	1 (2%)	3 (4%)		
Smoking status	N=38	N=194	3.99	0.003
Smoker	9 (24%)	6 (3%)	(1.58 – 10.05)	
Non-smoker	29 (76%)	188 (97%)		
Number of previous caesarean sections	N=48	N=193	1.83 (1.29 – 2.59)	0.001
1	23 (48%)	147 (76%)		
2	17 (35%)	32 (16.5%)		
≥ 3	8 (16%)	14 (7.5%)		
Previous uterine surgery	N=47	N=183	0.78	0.569
Yes	5 (11%)	42 (8%)	(0.41 – 3.33)	
No	42 (89%)	168 (91%)		
Medical problems	59	67	0.46 (0.21-0.99)	0.05
Yes	14 (23%)	27 (40%)		
No	45 (76%)	40 (60%)		

*live births

**Data presented and analysed according to available data (missing data not included)

Diagnosis

The mean age at presentation was 35 years (±4.8). The most common symptom at presentation was vaginal bleeding (46%), followed by vaginal bleeding and pain (27%), pain (6%) and the remaining were asymptomatic (Table 5). The mean gestational age at presentation was 9 weeks (range 6-18 weeks).

Table 5. Presenting features in women diagnosed with a CSP

Presentation	**(n=41)**
Gestation at presentation	Mean 9 weeks (range= 6-18)
Symptoms	
Vaginal bleeding	19 (46%)
Pain	6 (15%)
Vaginal bleeding and pain	11 (27%)
Asymptomatic	5 (12%)

Ultrasonography was performed in 44/48 (92%) women. Data was missing for 4 women. Thirty three (75%) women had a transvaginal ultrasound scan, 10 (23%) had transabdominal ultrasound scan, and 1 (3%) woman had both transavaginal and transabdmonial ultrasonography. The main findings on ultrasound scan are summarised in Table 6.

Table 6. Ultrasound findings in women diagnosed with CSP

Ultrasound features (n=44)*	**Seen**	**Not seen**	**Not assessed/ not reported**
Presence of gestational sac	40 (91%)	4(9%)	0
Pregnancy invading into the myometrium	33 (75%)	10 (23%)	1 (2%)
Sustained peritrophoblastic circulation	21 (48%)	3 (7%)	20 (45%)
Negative sliding organ sign	25 (57%)	1 (2%)	18 (41%)
Herniation of gestational sac	9 (21%)	34 (77%)	1 (2%)
Cardiac activity present	14 (32%)	26 (59%)	4 (9%)
Uterine cavity empty	25 (57%)	16 (36%)	3 (7%)
Closed internal os	34 (77%)	3 (7%)	7 (16%)
Intact endometrium	23 (52%)	5 (11%)	16 (36%)
Concomittant IUP	3 (7%)	40 (91%)	1 (2%)

IUP=Intrauterine pregnancy. * Cases with complete data (Total number of women n= 48, details in 4 women not reported).

Additional investigations

24 women had serial BhCG measurement(s), 6 women had MRI assessment, 8 women had 3D ultrasonography, and 3 women had diagnostic laparoscopy. Diagnostic hysteroscopy was not used in any of the women. Furthermore, none of the cases were investigated by CT scan.

Outcomes

The treatment outcomes are presented in Table 7. Sixty one percent (30/49) of women presenting with CSP had surgical treatment as primary management of caesarean ectopic pregnancy. This was followed by expectant management (10/49, 20.4%) and medical management (9/49, 18.4%).

Dilatation and curettage (including those reported as suction curettage) was the predominant surgical approach (29/30). In 22/29 (76%) cases additional haemostatic measures were used, including misoprostol (15/22, 68%), syntometrine (10/22, 45%), foley catheter (3/22, 14%), shirodkar suture (5/22, 23%), embolization (2/22, 9%).

Methotrexate (MTX) was used in all (9/9, 100%) cases treated by medical management. In 8/9 women methotrexate was given by the intramuscular route at a dose of 85 – 110mg. In one case, MTX was given intrasac at a dose of 20mg.

Treatment success

Surgical management resulted in successful treatment of caesarean scar pregnancy in 26/28 (93%) cases (OR 0.07, 95% CI 0.01 – 0.49, *p*=0.007). Outcome data were missing for two women were reported to have had surgical treatment. Only half (4/8, 50%) of the cases who underwent primary medical treatment were successfully managed (OR 0.8, 95% CI 0.12 -5.4, *p*=0.8) with the rest (4/8) requiring further interventions; three women had surgical management as secondary treatment and one woman had repeat medical treatment. Data was missing for one woman and it is not clear whether additional treatment was given. Expectant management was

associated with the highest failure rate, with 66% of women requiring further treatment. Multivariate analysis of successful outcome by treatment approach, controlling for number of previous caesarean sections and parity, showed a statistically significant increase in the success rate in women treated with surgical treatment (aOR 0.03, 95% CI 0.001 – 0.5, *p*= 0.02).

Complications

Expectant management had the highest rate of complications (5/8, 50%) when compared with medical (3/8, 37.5%) and surgical treatment (11/29, 37.9%).

Bleeding was the most common complication (3/8, 37.5%) associated with expectant management. One woman was managed conservatively with BhCG follow-up. BhCG at presentation was 34,947 mIU/ml and fell to 166mIU/ml after 8 weeks. Due to persistent spotting, and multiple hospital visits as a result of retained products of conception, evident on ultrasound scan, a decision between the clinician and the woman was made to perform a surgical dilatation and curettage under ultrasound guidance. In theatre, the patient had an estimated blood loss of 2500ml and was given FFP, tranexamic acid and transfused 2 units of blood. She also underwent bilateral uterine artery emobilisation. She was given 48 hours of IV antibiotics and completed a course of oral antibiotics. Another woman was managed conservatively and underwent a planned caesarean section at 33 weeks gestation. The baby was born alive and healthy. In theatre she was diagnosed with a placenta percreta and suffered an estimated 2200ml blood loss. An emergency hysterectomy was

performed. A vascular surgeon was also called to theatre and a uterine artery embolization was performed. Postoperative haemoglobin was 6g/dl.

Medical treatment was associated with the highest rate of retained products of conception (25%) compared with surgical (0%) and expectant (12.5%). The most frequent complication following surgical management was bleeding (8/29, 27.5%), followed by infection (2/29, 6.9%). Two women who were reported to have had bleeding as a complication of surgical treatment had in fact undergone emergency caesarean sections as primary surgical management for ongoing scar pregnancy. One woman presented with sepsis and bleeding at 34 weeks and underwent an emergency caesarean section. The estimated blood loss was 500ml. The baby was born alive and healthy. The other woman had an emergency caesarean section at 30 weeks gestation with premature rupture of membranes and sepsis secondary to chorioamnionitis. She was found to have placenta percreta at caesarean section had a 9500ml blood loss, requiring 20 units of blood transfusion. A subtotal hysterectomy was performed. The baby was born alive with apgars of 1 and 6 at 1min and 5mins respectively, and required admission to neonatal unit.

None of the women suffered uterine scar rupture following treatment. Logistic regression using expectant management as baseline showed no difference in the risk of bleeding between the groups. It was not possible to adjust for the rest of the complications due to the small sample size.

Table 7. Outcome data for each treatment group

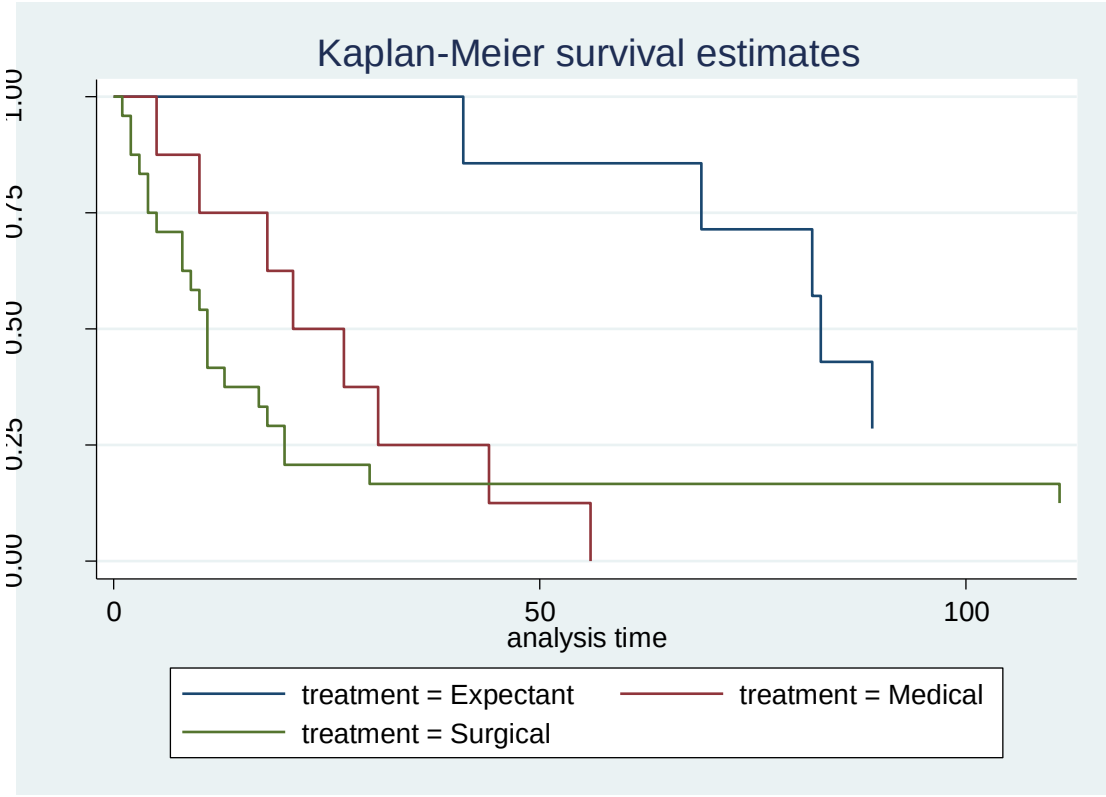
Outcomes	Expectant	Medical	Surgical	Unadjusted OR (95% CI)	*P*	Adjusted* OR (95% CI)
Treatment success**	4/9 (44.4%)	4/8 (50%)	26/28 (93%)			
Expectant vs Medical				0.8 (0.12–5.4)	0.8	1.02 (0.09 – 11.97)
Expectant vs Surgical				0.07 (0.01–0.49)	0.007	0.03 (0.001 – 0.51)
Complications	5/8 (50%)	3/8(37.5%)	11/29(37.9%)			
Overall						
Expectant vs Medical				1.67 (0.23-12.22)	0.62	NA
Expectant vs Surgical				1.64 (0.34-7.91)	0.54	NA
Bleeding	3/8 (37.5%)	1/8(12.5%)	8/29 (27.5%)			
Expectant vs Medical				4.2 (0.33 – 53.1)	0.27	NA
Expectant vs Surgical				1.58 (0.30 – 8.17)	0.59	NA
RPOC	1/8 (12.5%)	2/8 (25%)	0/29 (0%)	NA	NA	NA
Infection	0/8 (0%)	0/8 (0%)	2/29 (6.9%)	NA	NA	NA
Uterine scar rupture	0/8 (0%)	0/8 (0%)	0/29	NA	NA	NA
Hysterectomy	1/8 (12.5%)	0/8 (0%)	1/29 (3.4%)	NA	NA	NA
Discharge from care	7/10 (70%)***	9/9 (100%)	29/29 (100%)			
Expectant vs Medical				NA	NA	NA
Expectant vs Surgical				0.08 (0.01-0.51)	0.008	0.15 (0.02-1.44)
Follow-up duration****	96 (82-83)	27 (21-27)	35 (3-111)			
Expectant vs Medical				3.3 (1.05 -10.42)	0.04	NA
Expectant vs Surgical				3.6 (1.34 - 9.69)	0.01	NA

*Adjusted for parity and number of CS. **Defined as resolution of CSP without the need for additional interventions. *** 3 women remain under follow up for ongoing pregnancy. **** in days, (IQR). NA= Not Applicable (where it was not possible to compute due to small numbers)

Follow-up

The median length of follow-up (figure 26) in women treated with expectant management was 96 days (IQR 82 - 83, range 38-233), compared with 26.5 days (IQR 21 - 27, range 5-56) in medical management and 34.5 days (IQR 3 - 111, range 1-180) following surgical management. 70% (7/10) of women managed expectantly have been discharged from care; five women had resolution of pregnancy and two women had live births following planned caesarean sections at 33 and 39 weeks. Three women remain under follow up for ongoing pregnancy. All women (9/9, 100%) treated with medical management as well as all women treated surgically (28/28, 100%) have been discharged from care. Although reported to have had surgical treatment as primary management, one woman had in fact been managed conservatively for 8 weeks with BhCG follow up prior to surgical management, and this is likely to have skewed the follow-up interval.

Figure 26. Kaplan-Meier survival curve for resolution of CSP according to treatment group



DISCUSSION

This study estimates a UK incidence of caesarean scar pregnancy of 1 per 10 000 maternities (95 % CI, 0.71 – 1.19). This equates to one case every two years in a unit delivering 5000 women. Although rare, CSP is not confined to tertiary centres and is managed in many district general hospitals.

The main findings of this study are that maternal age (>35 years), previous caesarean sections (≥2), smoking and parity (2 or more live births) are prognostic predictors of having a caesarean scar pregnancy. The current treatment options of expectant, medical and surgical treatment are widely used in practice for the management of caesarean scar pregnancy. Surgical management is the first line approach in the majority of cases. Expectant management is opted for more frequently by women than medical management. Expectant management is associated with a high risk of bleeding, need for emergency surgery and hysterectomy. Medical treatment appears to be ineffective, with 50% of cases requiring further interventions for persistent mass (retained products of conception). Surgical management was found to have a high success rate but appeared to have a higher risk of bleeding than medical management although this was not statistically significant and the overall complication rates were comparable in both groups.

The findings of this study in this chapter are limited by a number of factors. The study protocol defines the study methodology, and details the strategies used for the identification of cases as well as the methods for data collection. Issues regarding the ascertainment of diagnosis have been previously discussed.

Despite multiple attempts to request the original data from reporting units, it was not possible to obtain complete data for all reported cases. This was a limitation which arose from reporting centres across the UK, and not limited to a specific region or unit. It is possible that analyses with the missing data may have shown a difference in the study findings. However, the analyses based on the available data were unbiased, although based on a smaller sample size than the original data set. The use of a smaller sample size could show an underestimate or overestimate of effects. Continued attempts will be made to obtain this data prior to study publication.

Our data showed an increased risk of major obstetric haemorrhage (4/4, 100%), delivery prior to 37 weeks gestation (3/4, 75%), emergency caesarean section for delivery (2/4, 50%) and emergency hysterectomy (2/4, 50%) in women with ongoing pregnancy. All babies were born alive, with 1/4 (25%) requiring admission to neonatal unit.

Where diagnostic modality was reported, all women (44/44) had an ultrasound scan. It is possible that false positive cases have been reported as a caesarean scar pregnancy. Indeed 2 cases were excluded from the study as they were initially thought to be CSP but later confirmed to be a failing pregnancy in one case and a cervical pregnancy in another. Included cases were assessed objectively against a diagnostic criteria for CSP proposed by Jurkovic et al.(41) In 6 women, MRI was used in addition to transvaginal scanning, however, the benefit of MRI assessment for the diagnosis of CSP is unclear. Serum BhCG was measured in 24 women, and was predominantly used for monitoring purposes in the follow up period.

Analysis showed that a history of 2 or more previous caesarean sections is strongly associated with a risk of having a scar pregnancy. As the numbers were limited, it was not possible to assess the risk of having a CSP by number of previous CS. Nonetheless, with increasing number of caesarean deliveries the risk of abnormal placentation increases with subsequent pregnancy. Placenta accreta was reported in 2/48 (4%) women in our cohort, diagnosed at the time of caesarean section in 2 of the 4 women (50%) who chose to continue with their pregnancy. At present, making an antenatal diagnosis of placenta accreta is not reliable. A national cohort study (62) conducted by UKOSS on multiple repeat caesarean section (MRCS) in the UK found that 73% of women who had placenta praevia also had placenta accreta. The recommendation was that clinicians should regard any woman having MRCS diagnosed with an anterior placenta praevia as having a placenta accreta, unless otherwise demonstrated.

As with any medical condition, women should be fully counselled about the benefits and risks of all treatment options, and their decision should be respected and supported by the care provider. Pre-pregnancy counselling is important and should be given to all women with a history of caesarean section delivery regarding the risks of future pregnancies. Although the number of cases in this study are limited, this is the only population-wide prospective study of caesarean scar pregnancy in the UK and it is hoped that the findings of this study will aid women and clinicians in the decision on best treatment option.

SECTION 2

SYSTEMATIC REVIEWS OF PRIORITY QUESTIONS

IN MISCARRIAGE

CHAPTER 6

PROGESTOGEN FOR THE TREATMENT OF EARLY PREGNANCY BLEEDING: A SYSTEMATIC REVIEW AND META-ANALYSIS

OBJECTIVES

1. To determine the effectiveness of progestogens to reduce miscarriage in women presenting with early pregnancy bleeding
2. To identify adverse effects associated with progestogen use

ABSTRACT

Objective

To determine the effectiveness of progestogen treatment for the reduction of miscarriage in women presenting with early pregnancy bleeding.

Methods

Studies were identified without language restrictions from MEDLINE (1966-2013), EMBASE (1980-2013), Cochrane Library, and manual searching of bibliographies of known primary and review articles. Studies were selected if progestogen treatment was given to women presenting with early pregnancy and if studies reported miscarriage rate. Only studies of randomised trials were included. Data were extracted on study characteristics, quality and the primary outcome of interest. Relative risks from individual studies were meta-analysed using random and fixed effects model as. Heterogeneity evaluated graphically using forest plots and statistically using the I^2 statistic.

Results

The search identified 7 randomised trials comprising 744 women. Meta-analysis of these seven studies showed a statistically significant reduction in miscarriage rate with progestogen use (RR 0.53, 95% CI: 0.39 to 0.73). There was no heterogeneity across the studies (I^2=0%, p=0.81), suggesting consistency across the studies. Quality assessment of the studies showed poor methodological quality, with none of the studies reporting the method of allocation concealment, only 3/7 were placebo-controlled, and 5/7 studies were not blinded.

Conclusion

There is evidence to suggest that progestogen treatment in women presenting with early pregnancy bleeding can reduce the risk of miscarriage. Existing trials are small and of poor methodological quality limiting the confidence in the findings of this review. A large high quality randomised trial is needed to robustly address this question.

INTRODUCTION

Threatened miscarriage is the most common complication of early pregnancy, occurring in approximately 20% of pregnant women before 20 weeks of gestation. (63)

Miscarriage remains an important cause of morbidity and mortality, especially in low-income countries. (64) The great majority of miscarriages occur early before 12 weeks, and less than 5% occur after fetal heart activity is identified. (65) Approximately half of all miscarriages are associated with fetal chromosomal abnormality, particularly in those of earlier gestational demise, however the cause in the remainder is unclear. (66;67)

Low progesterone levels have been linked to an increased risk of first trimester miscarriage. (68) Progesterone is a natural hormone, which is secreted in women principally by the corpus luteum in the ovaries during the normal menstrual cycle as well as during the first two months of pregnancy, after which production shifts to the placenta. Progesterone is derived from cholesterol steroids. It has different actions depending on the stage in the oestrous cycle. Progesterone regulates maturation of the oocytes, ovulation, myometrial quiescence, mammary gland growth and endometrial enzymes. (69;70) Progesterone exerts other wide-ranging actions including effects on metabolism, (71) respiratory system (72) and central nervous system (73).

Progesterone is a well-established drug substance that has been used clinically since the 1980s. It is used widely in assisted conception. (74;75)

Studies have shown that low progesterone is found in women with failing pregnancies and it is in these women that progesterone might be expected to have an effect. Given the recognised role of progesterone in maintaining pregnancy, progestogens have been used for many decades in an attempt to salvage threatened pregnancies. (76) This rationale is supported by the effectiveness of progesterone antagonists like mifepristone to terminate pregnancies. (77)

Recently, Haas et al (78) conducted a meta-analysis of progestogen use for the prevention of miscarriage. The findings of their review suggested that progestogen is not effective in the prevention of miscarriage. The population they included was heterogeneous, including women who predominantly presented *without* vaginal bleeding, and who were given progestogen treatment for the *prevention* rather than the treatment of threatened miscarriage. The majority of the included women had a history of recurrent miscarriages, and did not present with early pregnancy bleeding. Therefore their review did not address the question of whether progestogen is effective in reducing miscarriage risk in women presenting with early pregnancy bleeding.

The aim of this review is to systematically review studies on the effectiveness of progestogens for the treatment of threatened miscarriage.

METHODS

Identification of studies

I searched MEDLINE (1966-2014), EMBASE (1980-2014), Cochrane Library, and Conference Proceedings (ISI Proceedings, 1990-2014) for relevant citations. In

MEDLINE, a combination of Medical Subject Headings (MeSH) and textwords were used to generate two subsets of citations, one including studies of progestogen (‘progesterone’, ‘progestogen’ , ‘dydrogesterone’ , ‘duphaston’) and the other studies of miscarriage (miscarriage, abortion, ‘early pregnancy’, bleeding). These subsets were combined using ‘AND’ to generate a subset of citations relevant to the research question. Where necessary, this search strategy was adapted for use in the other electronic databases. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Articles frequently cited were used in the Science Citation Index to identify additional citations. I also made enquiries about unpublished studies from researchers investigating in this field.

Study selection

Studies in which progestogen therapy was used for the treatment of early pregnancy bleeding were selected in a two-stage process. First, the electronic searches were scrutinised and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of these manuscripts. In case of duplicate publication, the most recent and complete versions were selected. There were no language restrictions but studies with case-control or cohort design were excluded. Information was extracted from each selected article on study characteristics, quality and miscarriage rate.

Methodological quality assessment

All manuscripts meeting the selection criteria were assessed for their methodological

quality. Quality was defined as the confidence that the study design, conduct and analysis minimised bias. Quality assessment was carried out using the Cochrane collaboration tool, which assesses the risk of bias through examining the following items; random sequence generation, allocation concealment, blinding of participants and personnel, and of the outcome assessment, completeness of outcome data, selective reporting and anyother bias within the studies.

Each trial was assessed on the method of randomisation, whether it was double blind and whether there was a description of withdrawals and dropouts. Additionally, I assessed the quality of allocation concealment. A study was considered to be of good quality if participants were appropriately randomised, if blinding of participants and study personnel was adequate, if the method of allocation concealment was adequate, and if all participants were accounted for.

Data extraction

I designed a data extraction form to extract relevant data. A second reviewer (AC) extracted data using the agreed form. Any discrepancies were resolved by discussion.

Data synthesis

I carried out statistical analyses using the Review Manager software (RevMan 5.3). Relative risks with 95% confidence intervals from each study were combined for meta-analysis using the Peto-modified Mantel-Haenszel method. The fixed-effect

model for combining data was used where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where clinical heterogeneity was deemed significant to expect that the underlying treatment effects differ between trials, or where I detected substantial statistical heterogeneity, I used random-effects meta-analysis to produce an overall summary of an average treatment effect across trials.

Heterogeneity was assessed graphically using forest plot and statistically using chi-squared test. To detect publication and related biases, I undertook funnel plot analysis using Egger's tests to evaluate for asymmetry.

RESULTS

Literature identification

Figure 27 provides a summary of the process of literature identification and selection. The search strategy yielded 150 citations. Of these, 117 publications were excluded as it was clear from the title or abstract that they did not fulfill the selection criteria. I obtained full manuscripts for the remaining 33 articles. Following scrutiny of these, 6 studies were excluded as they were not randomized trials, 3 studies did not report original data, in 4 studies treatment was commenced in the second or third trimester, 7 studies reported different outcomes, 2 studies had duplicate data and 4 studies used combined progestogen treatment (3 with oestrogen, 1 with immunotherapy). Therefore the total number of studies included in the review was 7.

Study characteristics

The seven studies (76;79-84) included a total of 744 women. The study characteristics, including number of women, type, dose and route of progestogen used, whether the trial was placebo controlled, and the reported outcomes are summarized in Table 8.

Quality of included studies

The quality of the included studies is summarised in Table 9. The studies were randomised or quasi-randomized trials which compared progestogens with placebo or no treatment, given for the treatment of miscarriage. These studies were small and of poor quality, with none reporting the method of allocation concealment. Only 3/7 studies were placebo-controlled, and 5/7 studies were not blinded.

Figure 27. Study selection process for systematic review of progestogen therapy for early pregnancy bleeding

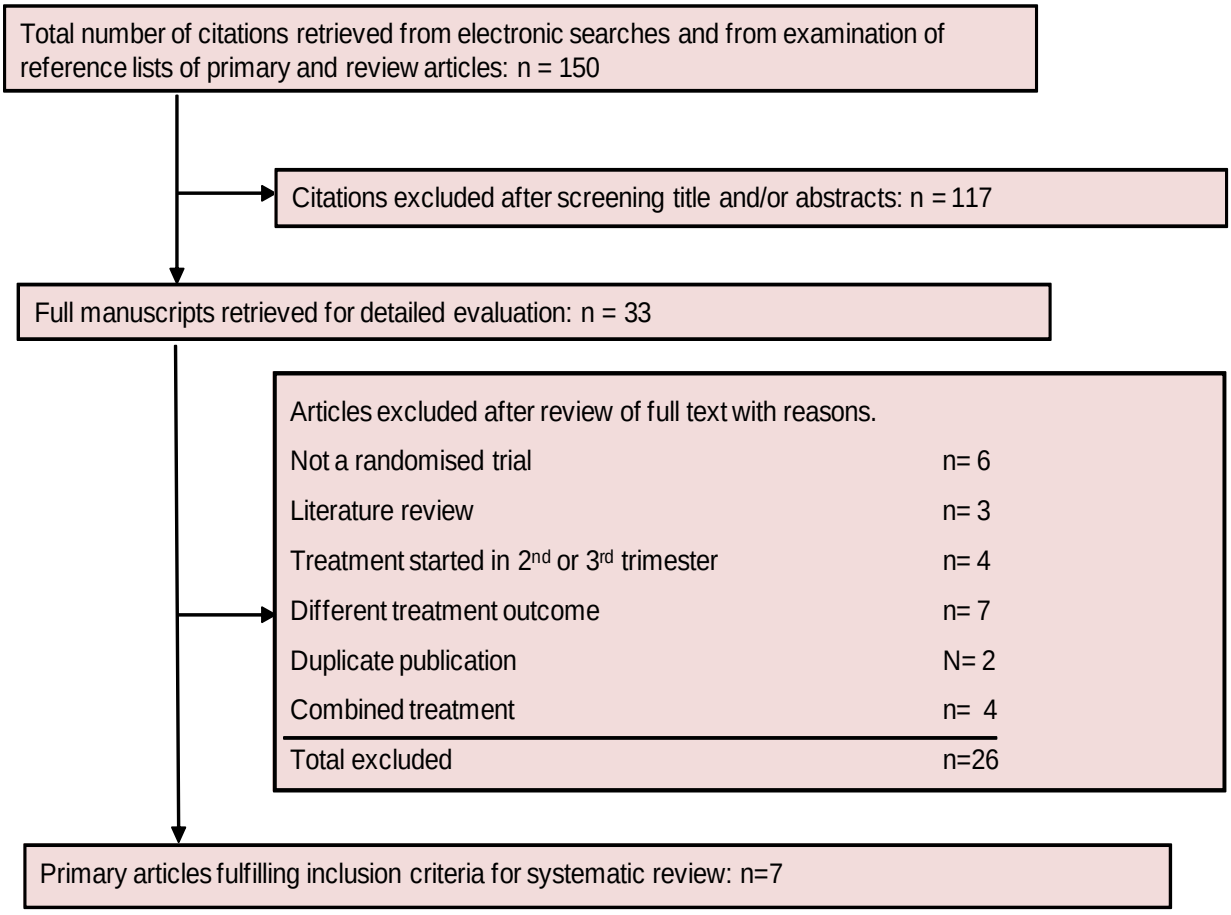


Table 8. Randomised trials of progestogens versus placebo or no treatment

Study	Population	Intervention			Comparison	Outcome
		Route	*Dose*	*Duration*		
Misto 1967 ***n*=25**	Women presenting at different gestational age with threatened miscarriage	Oral (Dydrogesterone)	20-40mg	Once daily for 6-15 sometimes for longer periods and for several cycles	Placebo	Miscarriage
Ehrenskjold 1967 ***n*=153**	Women who wanted to continue their pregnancy, had a positive pregnancy test at admission or the day after and not aborted within the first treatment day included	Oral (Dyrdrogesterone)	20mg	20mg then staggered dose (20mg after 12hours/20mg every 8 hours until symptoms ceased/10mg am and pm for 5 days/5mg am and pm for at least 7 days	No treatment	Miscarriage rate Premature births Live births
Gerhard 1987 ***n*=34**	Women with confirmation of fetal viability by ultrasound before commencement of treatment	Vaginal suppository	25mg twice daily	Until the woman either miscarried or 14 days after bleeding stopped	Placebo	Miscarriage Birth weight Preterm labour
Palagiano 2004 ***n*=50**	Women with previous diagnosis of inadequate luteal phase, threatened miscarriage, and confirmed fetal viability. Gestational age 6-12 weeks	Vaginal suppository (Crinone 8%)	90mg OD	5 days Women followed up for 60 days for the occurrence of miscarriage and for 5 days for the other outcomes	Placebo	Pain relief Miscarriage Frequency of uterine contractions Blood loss

Omar 2005 ***n*=154**	Women presenting at 13 weeks or less with vaginal bleeding or spotting and USS confirmed foetal viability	Oral (Dydrogesterone)	40mg stat	40mg stat dose followed by 10mg twice daily until bleeding stopped	No treatment	Miscarriage
El-Zibdeh 2009 ***n*=146**	Women presenting at 5-8 weeks gestation, with mild to moderate vaginal bleeding	Oral (Dydrogesterone)	10mg twice daily	Continued until 1 week after bleeding stopped	No treatment	Miscarriage, preterm labour, congenital malformations, antepartum haemorrhage, preeclampsia, and intrauterine growth restriction
Pandian 2009 ***n*=191**	Women presenting between 5 and 16 weeks gestation	Oral (Dydrogesterone)	40mg stat	40mg stat followed by 10mg twice daily and continued until 16 weeks of gestation	No treatment	Miscarriage, preterm labour, congenital anomalies, antepartum haemorrhage, placenta praevia, caesarean section rate, pre-eclampsia, and intrauterine fetal death

Table 9. Risk of Bias in RCTs using the Cochrane collaboration risk of bias tool

Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Misto 1967					
Unclear	Low	Low	Unclear	Unclear	Unclear
Ehrenskjold 1967					
Unclear	Low	Low	Low	Unclear	Unclear
Gerhard 1987					
Unclear	Unclear	Low	Low	Low	Unclear
Palagiano 2004					
Unclear	Low	High	High	Unclear	High
Omar 2005					
Unclear	High	High	High	Unclear	Unclear
El-Zibdeh 2009					
High	High	Unclear	Unclear	Low	Low
Pandian 2009					
Low	Low	High	High	Unclear	Unclear

Primary outcome

Miscarriage

Pooling of seven studies of progestogen use in women with early pregnancy bleeding showed a statistically significant reduction in miscarriage rate in the progestogen group when compared with placebo or no treatment (RR 0.53, 95% CI: 0.39, 0.73, p= 0.0001, Figure 28). There was no heterogeneity across the studies (I^2=0%, p=0.81), suggesting consistency across the studies.

Secondary outcomes

Congenital malformations

Pooling of results from 3 studies of progestogen use in women with early pregnancy bleeding did not show a difference in congenital malformations when compared to placebo or no treatment (RR=0.96, 95% CI 0.09–10.20, p=0.97, Figure 29).

Preterm labour

Pooling of results from 3 studies of progestogen use in women with early pregnancy bleeding did not show a difference in preterm labour when compared to placebo or no treatment (RR=0.91, 95% CI 0.39–2.09, p=0.82, Figure 30). There was little variation across studies as indicated by an I2 value of 0% (p=0.41).

Neonatal death

Pooling of results from 2 studies of progestogen use in women with early pregnancy bleeding did not show a difference neonatal death when compared to placebo or no treatment (RR=0.96, 95% CI 0.09–10.20, p=0.97, Figure 31).

Figure 28. Meta-analysis of studies of progesterone in women with early pregnancy bleeding for the outcome of miscarriage

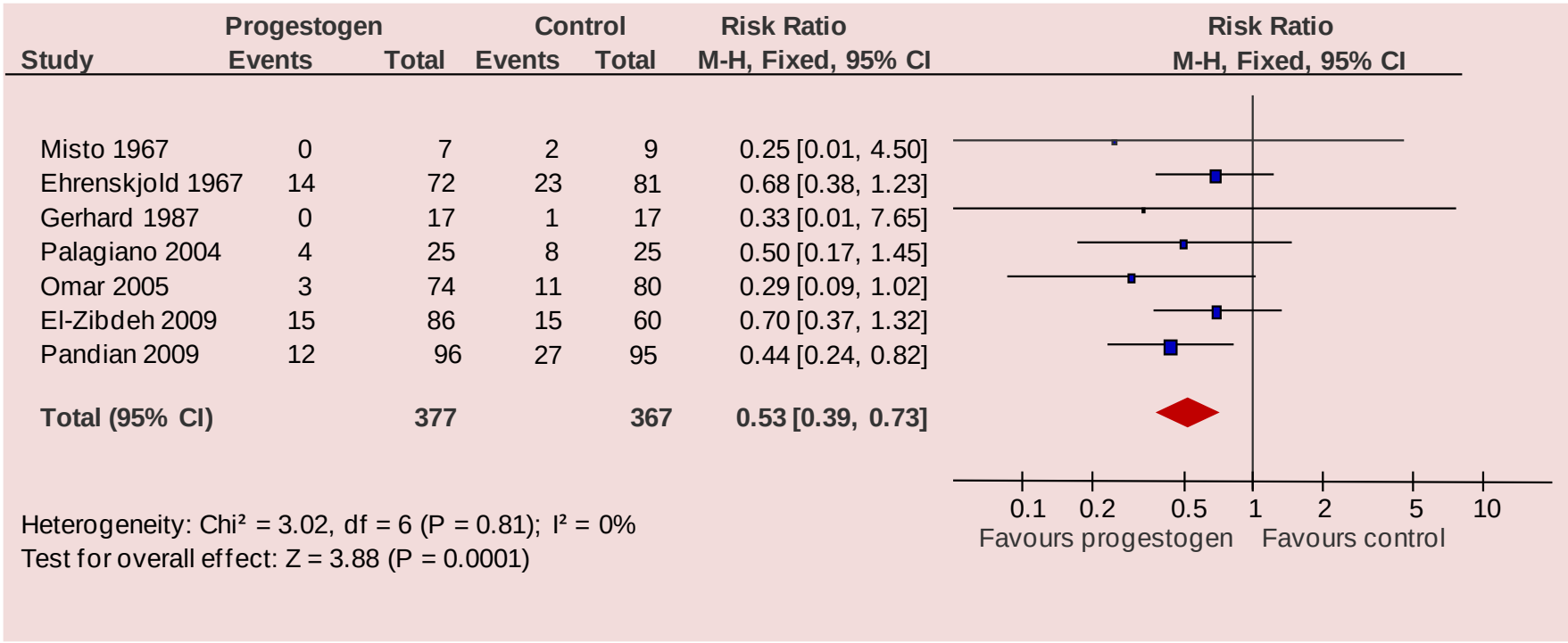


Figure 29. Meta-analysis of studies of progesterone in women with early pregnancy bleeding for the outcome of congenital anomalies

	Progesterone		Placebo or no treatment			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
El-Zibdeh 2009	2	71	1	34	100.0%	0.96 [0.09, 10.20]	
Gerhard 1987	0	23	0	21		Not estimable	
Pandian 2009	0	96	0	95		Not estimable	
Total (95% CI)		**190**		**150**	**100.0%**	**0.96 [0.09, 10.20]**	
Total events	2		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.04 (P = 0.97)							

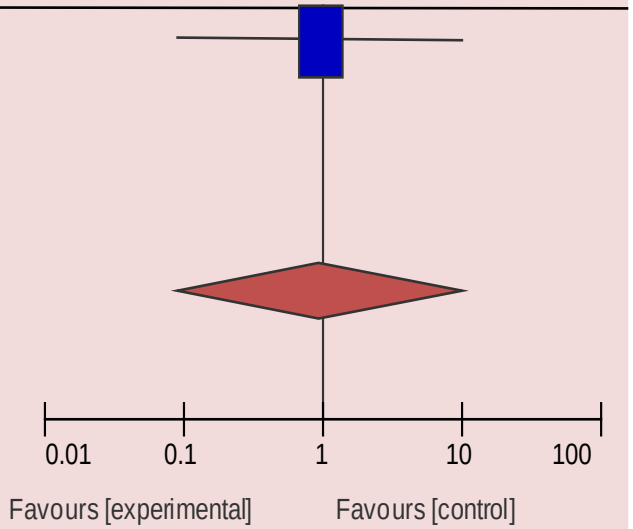


Figure 30. Meta-analysis of studies of progesterone in women with early pregnancy bleeding for the outcome of preterm labour

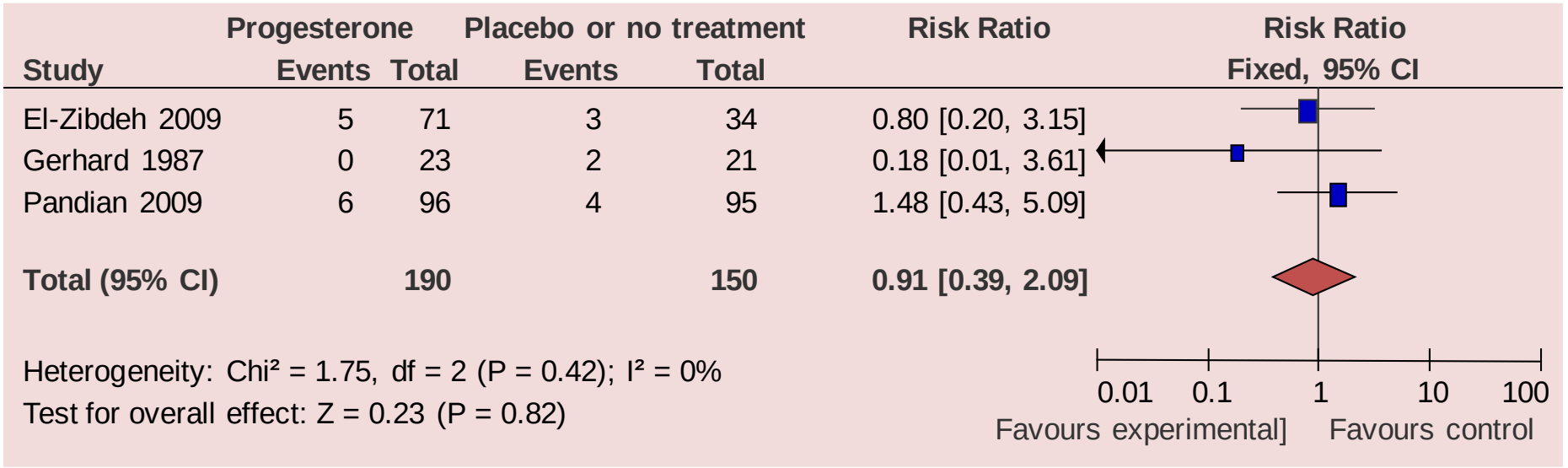


Figure 31. Meta-analysis of studies of progesterone in women with early pregnancy bleeding for the outcome of neonatal death

Secondary outcomes (continued)

Progestogen for the *prevention* of miscarriage in women with a history of recurrent miscarriages

History of 2 or more previous miscarriages

Pooling of results from 7 studies of progestogen treatment in pregnant women with a history of 2 or more recurrent miscarriages did not show a difference in miscarriage rate when compared to placebo or no treatment (RR=0.73, 95% CI 0.52–1.04, p=0.08). There was little variation across studies as indicated by an I2 value of 5% (p=0.38).

History of 3 or more previous miscarriages

Pooling of results from 4 studies of progestogen treatment in pregnant women with a history of 3 or more recurrent miscarriages showed a statistically significant reduction in miscarriage in the progestogen group when compared with placebo or no treatment (RR=0.39, 95% CI0.21–0.72, p=0.003). There was consistency across studies as indicated by an I2 value of 0% (p=0.98).

DISCUSSION

This systematic review, which included 7 studies, found that the use of progestogens for the treatment of early pregnancy bleeding is associated with a relative risk reduction in miscarriage by 47%. No difference was found in the risk of congenital anomalies, preterm birth or neonatal death.

There are several reasons that give strength to the findings of this study. Firstly, I performed an extensive search strategy and used valid data synthesis methods. No language restrictions were placed on the search or included study. Moreover, only studies of randomised design were included.

The weaknesses in the study are mainly related to the poor quality of the included studies. Although reported as randomised trials, the method of randomisation was unclear in 5 out of the 7 studies. In one study, participants were randomised according to the day of the week they presented to hospital. None of the studies reported the method of allocation concealment. Only 3/7 studies were placebo-controlled, and 5/7 studies were not blinded. Moreover, there was clinical heterogeneity between the trials. Women were treated for different durations; one study did not have a strict protocol for the duration of treatment, with some women having treatment for 6-15 days, whilst others were on progesterone for a longer unspecified period. Palagiano (76) treated women for 5 days, whilst other studies used bleeding cessation as the time point for ending treatment. Moreover, the dosage and routes varied between trials, with one trial using as little a dose as 25mg twice daily of progesterone vaginal suppositories. Furthermore, few of the studies used ultrasonography to confirm the pregnancy or fetal viability prior to enrolment to the study.

Despite the weaknesses of the included studies, a significant reduction in the risk of miscarriage was demonstrated in the progestogen group. Progesterone is thought to have an immune-modulatory effect on the uterus, and has a role in preventing

rejection of the embryo, enhancing uterine quiescence and suppressing uterine contractions. (70) Progesterone is used widely in the field of assisted conception. There have been some reports of an increase in hypospadias, however recent reviews have not demonstrated this. (85;86)

The findings of this review are consistent with the Cochrane review conducted by Wahabi et al. (86) Their review, which included 4 studies, found a reduction of up to 50% in women receiving oral progesterone (dydrogesterone). There was a trend towards a reduction in women receiving vaginal progesterone, however this did not reach statistical significance, probably due to the small sample size. Based on the findings of this review, NICE called for “A very large multicentre randomised controlled trial of women treated with either progesterone/progestogen or placebo should be conducted.”

The conclusions of this systematic review are limited by the poor methodological quality of the included studies and the small number of participants. In agreement with the call by NICE, a high quality randomized controlled trial is needed to robustly address this question.

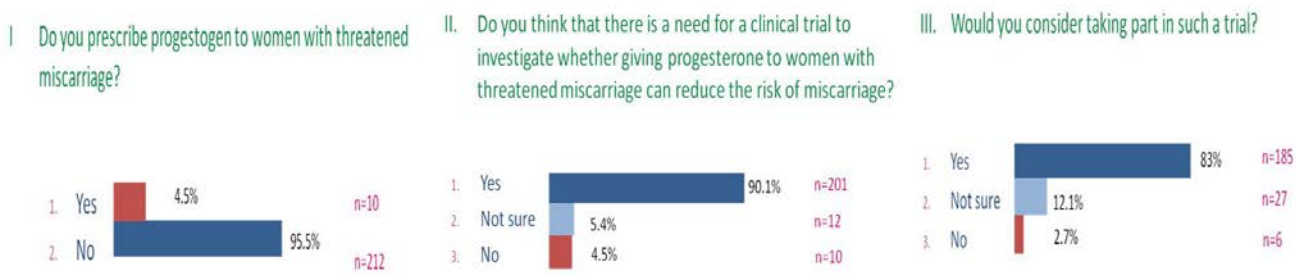
Clinician and patient surveys

To understand how the existing evidence is viewed by clinicians, I conducted UK and International Clinician surveys, the findings of which are provided below.

UK and International Clinician surveys

I conducted a ***UK*** clinician survey (n=222) in Oct 2012. In the UK, the vast majority of clinicians (212/222, 95.5%) do not use progesterone to prevent miscarriage in women with early pregnancy bleeding (Figure 32). The key reason for non-use is the lack of robust evidence. It is therefore not surprising that *the majority (201/222, 91%) called for a definitive trial*.

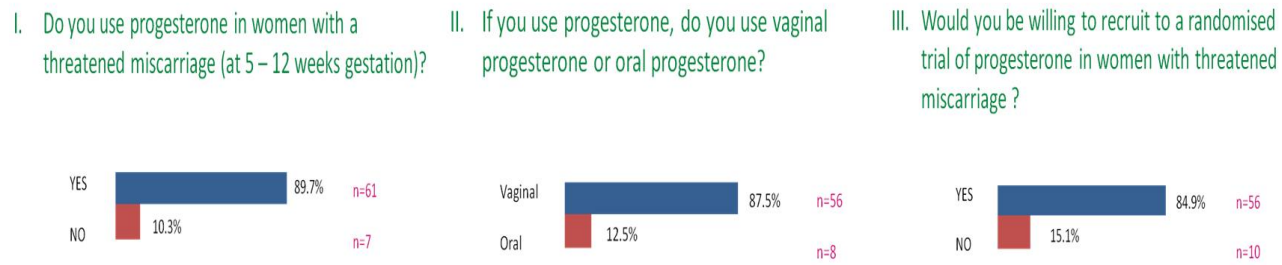
Figure 32. UK clinician survey findings



A survey of international practitioners was also conducted at FIGO (International Federation of Gynecology and Obstetrics) 2012 Conference, Rome. Surprisingly, this survey found the majority of clinicians (61/68, 90%) already use progesterone in women with early pregnancy bleeding, *although the vast majority (56/66, 85%) were*

willing to recruit into a randomised trial, (Figure 33) presumably indicating lack of confidence in the available evidence.

Figure 33. International clinician survey findings



UK patient survey

I conducted a survey to seek the opinion of women seen in the Early Pregnancy Unit (n=79) at Birmingham's Womens Hospital, in December 2012. The majority of women (57/79, 72%) said they would consider taking part in the trial, and 70% (55/79) found the vaginal route of administration acceptable. Furthermore, an independent survey was conducted by the Miscarriage Association to identify women's opinions on a double-blind placebo-controlled trial in early pregnancy and the acceptability of administering vaginal or rectal medications. The findings of this survey of 128 women showed that 91% (116/128) would enter or consider entering the trial. The vaginal route of administration of medicines was acceptable to 100/111 (90%) of women, and the rectal route acceptable to 91/111 (82%) of women.

CHAPTER 7

THE EFFECT OF PRESENCE AND TREATMENT OF HYDROSALPINX ON MISCARRIAGE: A SYSTEMATIC REVIEW AND META-ANALYSIS

OBJECTIVES

1. To evaluate the relationship between presence of hydrosalpinx and miscarriage
2. To evaluate the effects of management of hydrosalpinx on the risk of miscarriage

ABSTRACT

Objectives

To evaluate the association between the presence and management of hydrosalpinx on the risk of miscarriage (as opposed to the chances of conception of a pregnancy).

Search strategy

Searches were conducted on MEDLINE, EMBASE, Cochrane Library and Web of Science (inception- October 2014) in all languages, together with reference lists of retrieved papers. Studies comparing miscarriage rate in women with hydroaslpinx to women without hydrosalpinx were included. Furthermore, studies reporting miscarriage in women who underwent treatment of hydrosalpinx compared to no treatment were also included. Study selection was conducted independently by two reviewers. The Cochrane scale for randomised controlled trials and the Newcastle-Ottawa Quality Assessment Scale for cohort studies were used for quality assessment. Data extraction was conducted independently by two reviewers. Relative risks from individual studies were meta-analysed.

Results

Twenty three studies were identified, of which 7 were randomised controlled trials and 16 were observational studies, all in the IVF population. The studies scored well on the Cochrane and Newcastle-Ottawa scales for quality assessment. Meta-analysis of 14 observational studies showed a 64% relative increase in the risk of miscarriage in women with hydrosalpinx compared to women without hydrosalpinx

(RR=1.64, 95% CI 1.27, 2.12, p=0.0002, I2=31%). Pooling of results from 5 randomised controlled trials of treatment of hydrosalpinx with salpingectomy showed a halving in the risk of miscarriage in women who had salpingectomy for hydrosalpinx treatment when compared to women with untreated hydrosalpinx (RR=0.44, 95% CI 0.23- 0.83, *p*=0.01, p=0%). Similarly, pooling of results from 5 observational studies showed halving in the risk of miscarriage in women who had salpingectomy for hydrosalpinx in comparison to women with untreated hydrosalpinx (RR=0.49, 95% CI 0.34- 0.71, *p*=0.0002, I2=0%). No difference was found in women having ultrasound guided drainage (RR= 0.68, 95% CI 0.24- 1.95, *p*=0%).

Conclusion

There is evidence to suggest that the presence of hydrosalpinges increases the risk of miscarriage in IVF/ICSI pregnancies. Treatment for hydrosalpinges with salpingectomy can reduce the risk of miscarriage. These findings may have implications for women with a history of recurrent miscarriage, and raises the question whether routine screening for hydrosalpinx should be performed in this population. Further research is needed to assess this question.

INTRODUCTION

Hydrosalpinx is a fluid-filled distension of the fallopian tube in the presence of distal tubal occlusion. The incidence of hydrosalpinx within infertile women is between 10 to 13% when diagnosed by ultrasound. This figure increases to 30% with the use of hysterosalpingogram or laparoscopy (5). The most common pathogens associated with tubal damage is Chlamydia trachomatis . In vitro fertilization was first introduced as a method to overcome tubal infertility(1).

It has been widely established that the presence of hydrosalpinx is associated with lower implantation and pregnancy rates. Multiple studies have demonstrated that the presence of hydrosalpinges adversely affects IVF outcomes, with a reduction in live birth rates by approximately 50% (2, 3). Several mechanisms have been postulated to explain the adverse effects of hydrosalpinges on the live birth rate achieved with IVF, including direct embryotoxicity (5), a reduction in endometrial receptivity, and mechanical flushing of the embryo. Moreover, tt has also been demonstrated that treatment for hydrosalpinx can improve clinical pregnancy and live birth rate.

However, the question whether hydrosalpinx has a detrimental effect on an already established pregnancy, that is, when an intrauterine pregnancy is seen on ultrasonography has yet to be robustly reviewed. Moreover, the potential effectiveness of treatment in reducing miscarriage risk in such women is currently unknown. The aim of this review is to assess the effect of the presence and treatment of hydrosalpinx on miscarriage.

METHODS

Identification of literature and study selection

The population for this review is women with hydrosalpinx. The following electronic databases were searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science (inception - October 2014). A search strategy was carried out based on the following key words and/or medical subject heading (MeSH) terminology: hydrosalpinges, hydrosalpinx, abortion, spontaneous fetal loss, miscarriage, salpingectomy, salpingostomy, ultrasound guided aspiration. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. No language restrictions were placed in any of the searches or study selection.

I excluded articles where women had causes of infertility other than hydrosalpinx and where miscarriage was not reported as an outcome. Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinised by two reviewers independently (HH and FR) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publication, the most recent and complete versions were selected. Any disagreements about inclusion were resolved by consensus.

Quality assessment

All manuscripts meeting the selection criteria were assessed for their methodological quality. Quality was defined as the confidence that the study design, conduct and analysis minimised bias. Quality assessment was carried out using the Cochrane collaboration tool, which assesses the risk of bias through examining the following items; random sequence generation, allocation concealment, blinding of participants and personnel, and of the outcome assessment, completeness of outcome data, selective reporting and any other bias within the studies.

The Newcastle-Ottawa Quality Assessment was implemented for quality assessment of the included observational studies. This scale assesses eight components, including representativeness of the exposed cohort, selection of non-exposed cohort, ascertainment of exposure, outcome at start, comparability by design or analysis, outcome assessment, duration and adequacy of follow up . One star is awarded as maximum for all items except for comparability where a maximum of two stars can be awarded. I used an arbitrary score based on the assumption of equal weight of all items included in the Newcastle-Ottawa Scale. This was used to give a quantitative appraisal of overall quality of the individual studies. The score ranged from 0 to 9, with a score of either 0 or 1 for each item. From each study, outcome data were extracted in 2 x 2 tables by two reviewers HH and FR.

Data extraction

I designed a data extraction form to extract relevant data. A second reviewer (FR) extracted data using the agreed form. Any discrepancies were resolved by

discussion.

Data synthesis

For the analysis of miscarriage rates I analysed data per total number of pregnancies. I carried out statistical analyses using the Review Manager software (RevMan 5.3). Relative risks with 95% confidence intervals from each study were combined for meta-analysis using the Peto-modified Mantel-Haenszel method. The fixed-effect model for combining data was used where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where clinical heterogeneity was deemed significant to expect that the underlying treatment effects differ between trials, or where I detected substantial statistical heterogeneity, I used random-effects meta-analysis to produce an overall summary of an average treatment effect across trials.

Heterogeneity was assessed graphically using forest plot and statistically using chi-squared test. To detect publication and related biases, I undertook funnel plot analysis using Egger's tests to evaluate for asymmetry.

RESULTS

Literature identification

The search strategy yielded 2680 citations (Figure 34) of which 2512 publications were excluded because it was clear from the title or abstract that they did not fulfil the selection criteria. I obtained full manuscripts for the remaining articles. 145

publications were excluded because they did fulfil the inclusion criteria. Therefore the total number of studies included in the review was 23 (25;26;87-107). 7 of the included studies were of randomised controlled design (RCT) and 16 were observational studies.

Study characteristics

The characteristics of the studies are presented in Tables 10 and 11.

Quality assessment

The Cochrane and Newcastle-Ottawa scales for Quality Assessment are presented in Tables 12 and 13. The studies scored well on both scales. There was no evidence of publication bias on funnel-plot assessment.

Figure 34. Study selection process for the systematic review of hydrosalpinx and miscarriage

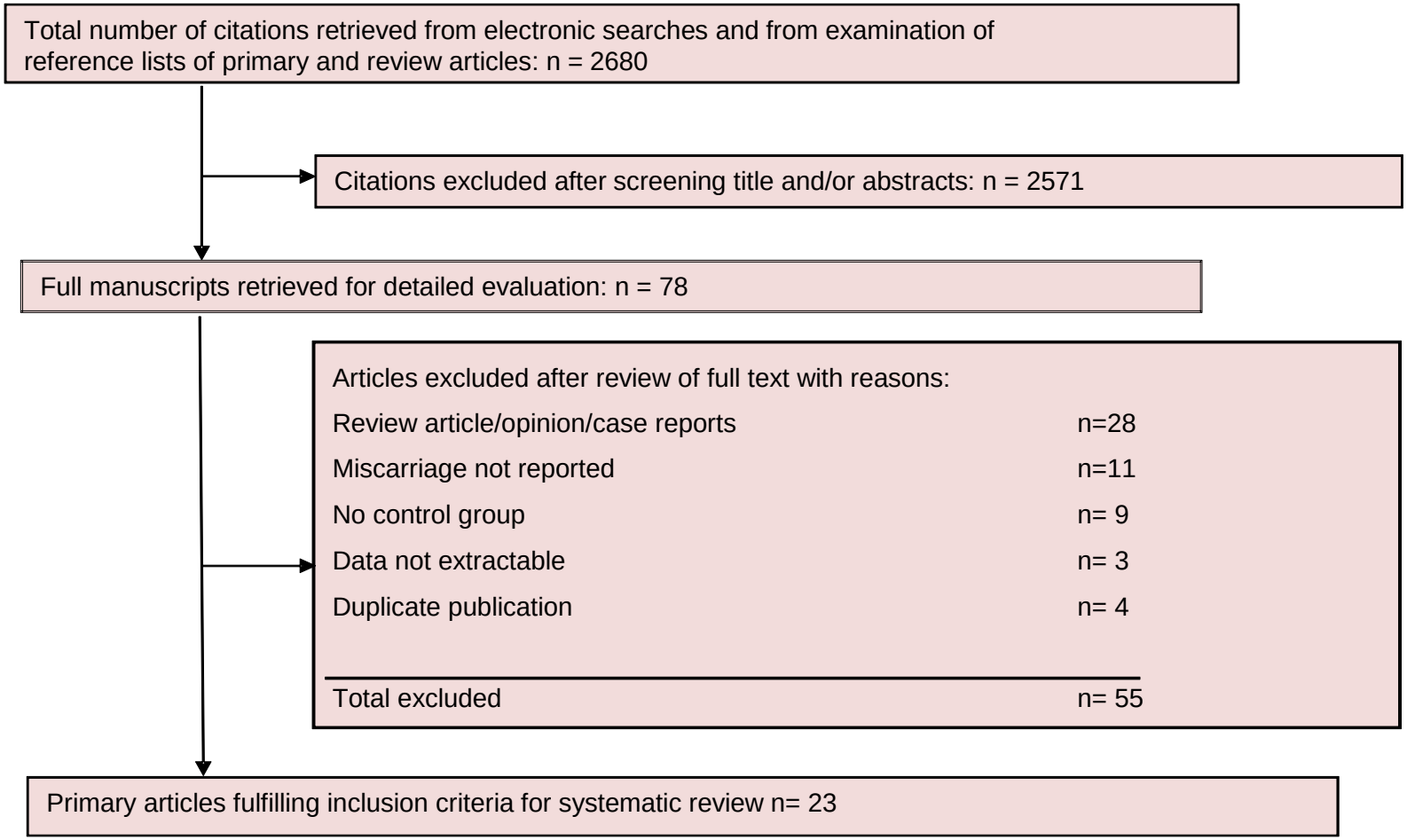


Table 10. Characteristics of studies of hydrosalpinx versus no hydrosalpinx in women undergoing IVF

Study	Population	Study groups	Outcomes	Study design
Blazar et al 1997	All patients who had undergone IVF for tubal factor at Brown University school of Medicine, Providence, Rhode Island between May 1988 and October 1994	Total 250 women Hydrosalpinx n= 67 Without Hydrosalpinx n= 183 Diagnosed on USS	Implantation rate, miscarriage and clinical pregnancy rate	Retrospective observational study
Akman et al 1996	All patients at The Women's Hospital Fertility Center at the Greater Baltimore Medical center, MD, USA, with tubal disease undergoing embryo transfer of previously cryopreserved embryo during a natural cycle between September 1993 and November 1995	Total 84 women Hydrosalpinx n= 10 Without Hydrosalpinx n= 74	Implantation rate, clinical pregnancy, miscarriage	Retrospective observational study

		Diagnosed on USS or HSG		
Andersen et al 1994	Results of first IVF treatment cycles in 144 patients from 1 January 1993 to 31 December 1995, who had tubal infertility only at ACU of Queen Mary Hospital, Hong Kong	Total 741 women Hydrosalpinx n= 62 No Hydrosalpinx n= 493 Diagnosed on USS	Implantation, miscarriage Pregnancy rate and delivery rate	Retrospective observational study
Hung-Yu Ng et al 1997	Women with tubal factor infertility who underwent IVF treatment at The New York Hospital –Cornell Medical Center between January 1989 to December 1995	Total 144 women Hydrosalpinx n= 43 Without Hydrosalpinx n=	Implantation rate, clinical pregnancy rate, miscarriage	Retrospective observational study

		101 Diagnosed on USS, HSG or laparoscopy		
Barmat et al 1999	Women with tubal factor infertility who underwent IVF-embryo transfer cyles at Nashville Fertility Center, USA between January 1993 and June 1996	Total 1000 women Hydrosalpinx n= 60 Without Hydrosalpinx n= 940 Diagnosed on Diagnosed on USS	Clinical pregnancy rate, miscarriage and live birth	Retrospective observational study

Freeman et al 2005	Women with and without who hydrosalpinx underwent IVF treatment in a university-based assisted reproduction programme	Total 286 women Hydrosalpinx n= 35 Without Hydrosalpinx n= 83 Diagnosed on USS or HSG	Implantation rate, clinical pregnancy rate, miscarriage	Retrospective observational study
Cohen et al 1999	Women with tubal factor infertility underwent IVF treatment at Micheal Reese Hospital and Fertility Center between January 1990 and December 1994	Total 110 women Hydrosalpinx= 10 Without Hydrosalpinx n= 100	Pregnancy, implantation, miscarriage and ectpic pregnancy rates.	Retrospective observational study

		Diagnosed on USS		
Sharara et al 1996	Women with tubal factor infertility who underwent IVF trearment at the Sahlgrenska University Hospital, Sweden between January 1990 and June 1993.	Total 123 women Hydrosalpinx= 63 No Hydrosalpinx n= 60 Diagnosed on USS	Implantation, pregnancy and miscarriage rates	Retrospective observational study
Strandell et al 1994	Women with tubal disease initiated on a stimulation cycle for eventual IVF between October 12 1987 and March 31 1995 at The women's fertility center, Greater Baltimore Medical Centre	Total 254 women Hydrosalpinx= Without Hydrosalpinx =	Pregnancy, miscarriage and delivery rates.	Retrospective observational study

		Diagnosed on USS and HSG		
Katz et al, 1996	Women with tubal disease who underwent IVF treatment at University of Bristol IVF unit at the BUPA Hospital Bristol from July 1989 to June 1993	Total 891 women Hydrosalpinx n= 79 Diagnosed on USS, HSG or laparoscopy	Pregnancy, miscarriage and Implantation rates.	Retrospective observational study
Fleming et al, 1996	Women with hydrosalpinx who underwent IVF treatment at Free University Brussels, Belgium between March 1989 and June 1993	Total 277 women Hydrosalpinx n= 79 Without Hydrosalpinx n= 198 Diagnosed on USS	Clinical Pregnancy, miscarriage and live birth rates	Retrospective observational study

Vandromme et al, 1995	Women with hydrosalpinx undergoing IVF treatment compared with women tubal infertility from other causes.	Total 78 women Hydrosalpinx n= 37 Without hydrosalpinx n=41 Diagnosed on USS	Clinical pregnancy, miscarriage, ongoing pregnancy	Retrospective observational study
Sims et al, 1993 Abstract	Not available from published abstract	Hydrosalpinx n=118 Without hydrosalpinx n=823 Diagnosed on USS	Clinical pregnancy, miscarriage, ongoing pregnancy	Retrospective observational study

Table 11. Characteristics of studies of treatment vs no treatment of hydrosalpinx in women undergoing IVF

Study	Population	Intervention	Comparison	Outcome	Study design
Kassabji et al 1994 n=275	Women undergoing IVF treatment at The Jones Institute for Reproductive Medicine, East Virginia Medical school, USA between 1988 and 1992	Bilateral Salpingectomy n= 157	No treatment n=118	oocyte retrieval and implantation and pregnancy outcome	Retrospective cohort study
Shelton et al 1996 n=23	Women with hydrosalpinx and have had a repeated implantation failure and have had unilateral or bilateral salpingectomy	Unilateral or bilateral salpingectomy n= 8	No treatment n=15	Implantation, clinical pregnancy and ongoing pregnancy rates	Retrospective cohort study
Murray et al 1998 n= 38	All IVF-ET cycles in women with tubal factor infertility at The Shady Grove Fertility Centre, Rockville, USA	Unilateral or bilateral salpingectomy n= 12	No treatment n= 26	Implantation, clinical pregnancy, miscarriage, live birth rates	Retrospective cohort study

Strandell et al 1999 n=204	Women with hydrosalpinx were randomised to laproscopic salpingectomy or no intervention before IVF treatment in Scandinavia	Unilateral or bilateral salpingectomy n=116	No intervention n= 88	Clinical pregnancy, live birth	Randomised controlled study
Hammadieh et al 2008 n=66	66 women with hydrosalpinx were randomised before IVF treatment to U/S guided aspiration or no aspiration	Ultrasound aspiration n = 32	No aspiration n= 34	Pregnancy, implantation, spontaneous abortion, ectopic pregnancy and pelvic infection rates	Randomised controlled study
Zolghadri et al 2006 n=13	Women with recurrent miscarriage and a unilateral hydrosalpinx(diagnosed by U/S) randomised to tubal surgery and no intervention	Laparoscopic fulguration n= 7	No intervention n= 6	Continuation of pregnancy over the first trimester	Randomised controlled study

Dechaud et al 1998 n= 60	Patients with tubal factor infertility (laparoscopic salpingectomy and no salpingectomy) and had IVF treatment	Laparoscopic salpingectomy n=30	No salpingectomy n= 30	Implantation rate and ongoing pregnancy rate	Pilot randomised study
Goldstein et al, n=31	Women aged 22 to 38 years with hydrosalpinx undergoing IVF treatment	Surgical treatment (selective salpingostomy-salpingectomy) n= 15	No surgical treatment n= 16	Pregnancy, spontaneous abortion, ectopic pregnancy and live birth rates	Randomised controlled study
Fouda and Sayed, 2010 n=110	Women with ultrasound visible hydrosalpinges who underwent IVF treatment at Ahmed Elgazzar Hospital, Cairo, between October 2006 and May 2010	Ultrasound guided aspiration of hydrosalpingeal fluid n=55	No treatment n= 55	Implantation, clinical pregnancy and ongoing pregnancy rate	Randomised controlled study

Kontoravdis et al 2006 n= 65	Women with unilateral or bilateral hydrosalpinges who underwent IVF treatment.	Salpingectomy = 50	No salpingectomy n= 15	Implantation, clinical pregnancy, ongoing pregnancy, miscarriage, and ectopic pregnancy rate.	Randomised controlled study

Table 12. Risk of Bias in RCTs using the Cochrane collaboration risk of bias tool

Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Dechaud 1998					
Unclear	Low	High	Low	Low	Low
Strandell 2001					
Low	Low	High	Low	Low	Low
Zolghadri 2006					
Low	Low	High	Low	Low	Low
Kontoravdis 2006					
Low	Low	High	Low	High	Low
Hammadieh 2008					
Low	High	High	Low	Low	Low

Table 13. Appraisal of methodological quality (Newcastle-Ottawa Scale) of included studies

Study	Case-cohort representative	Selection of non-exposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design§	Comparability by analysis	Outcome assessment	Duration of follow-up	Score
Akman, et al (1996)	*	*	*	*	*	*	*	*	8
Andersen, et al. (1994)	*	*	*	*	*	*	*	*	8
Barmat et al. (1999)	*	*	*	*	*	*	*	*	8
Blazar, et al. (1997)	*	*	*	*	*	*	*	*	8
Cohen, et al. (1999)	*	*	*	*	*	*	*	*	8
Freeman, et al. (1998)	*	*	*	*	*	*	*	*	8
Hung-Yu Ng, et al , (1997)	*	*	*	*	**	*	*	*	9
Sharara, et al, (1996)	*	*	*	*	*	*	*	*	8
Kassabji, et al, (1994)	*	*	*	*	*	*	*	*	8
Murray, et al,(1998)	*	*	*	*	*	*	*	*	8
Shelton,et al, (1996)	*	*	*	*	*	*	*	*	8
Strandell, et al, (1994)	*	*	*	*	*	*	*	*	8
Vandromme et al, (1995)	*	*	*	*	**	*	*	*	9

* - Indicates that feature is present; x- feature is absent. §-For comparability by design this checklist awards a maximum of two stars (**), one (*) or none if the feature is completely absent (x).

Primary outcome

Miscarriage (hydrosalpinx vs no hydrosalpinx)

Pooling of results from 14 observational studies showed a two-fold increase in the risk of miscarriage in women with hydrosalpinx compared to women without hydrosalpinx (RR=1.64, 95% CI 1.27, 2.12, p=0.0002, Figure 35). There was moderate variation across studies as indicated by an I^2 value of 31% (*p*=0.13).

Treatment vs no treatment (all interventions)

Pooling of results from 7 randomised controlled trials showed halving in the risk of miscarriage in women who had treatment for hydrosalpinges when compared to women with untreated hydrosalpinx (RR=0.49, 95% CI 0.29- 0.85, *p*=0.01, Figure 36). There was consistency across studies as indicated by an I^2 value of 0% (*p*=0.78).

By intervention

Salpingectomy

Pooling of results from 5 randomised trials that reported miscarriage as an outcome showed a 56% relative reduction in miscarriage in women who had salpingectomy for hydrosalpinx when compared with women with untreated hydrosalpinx (RR=0.44, 95% CI 0.23- 0.83, *p*=0.01, Figure 37). There was consistency across studies as indicated by an I^2 value of 0% (*p*=0.62).

Pooling of results from 5 observational studies showed a reduction in miscarriage in women who had salpingectomy for hydrosalpinx in comparison with women with

untreated hydrosalpinx (RR=0.49, 95% CI 0.34- 0.71, *p*=0.0002, Figure 38). There was consistency across studies as indicated by an I^2 value of 0% (*p*=0.75).

Ultrasound guided drainage

Pooling of results from 2 randomised controlled trials did not show a difference in miscarriage risk in women who had ultrasound guided drainage for hydrosalpinges when compared to women with untreated hydrosalpinx (RR= 0.68, 95% CI 0.24- 1.95, *p*=0.47%, Figure 39). There was consistency across studies as indicated by an I^2 value of 0% (*p*=0.96).

Figure 35. Meta-analysis of studies comparing miscarriage risk in women with hydrosalpinx to women with no hydrosalpinx

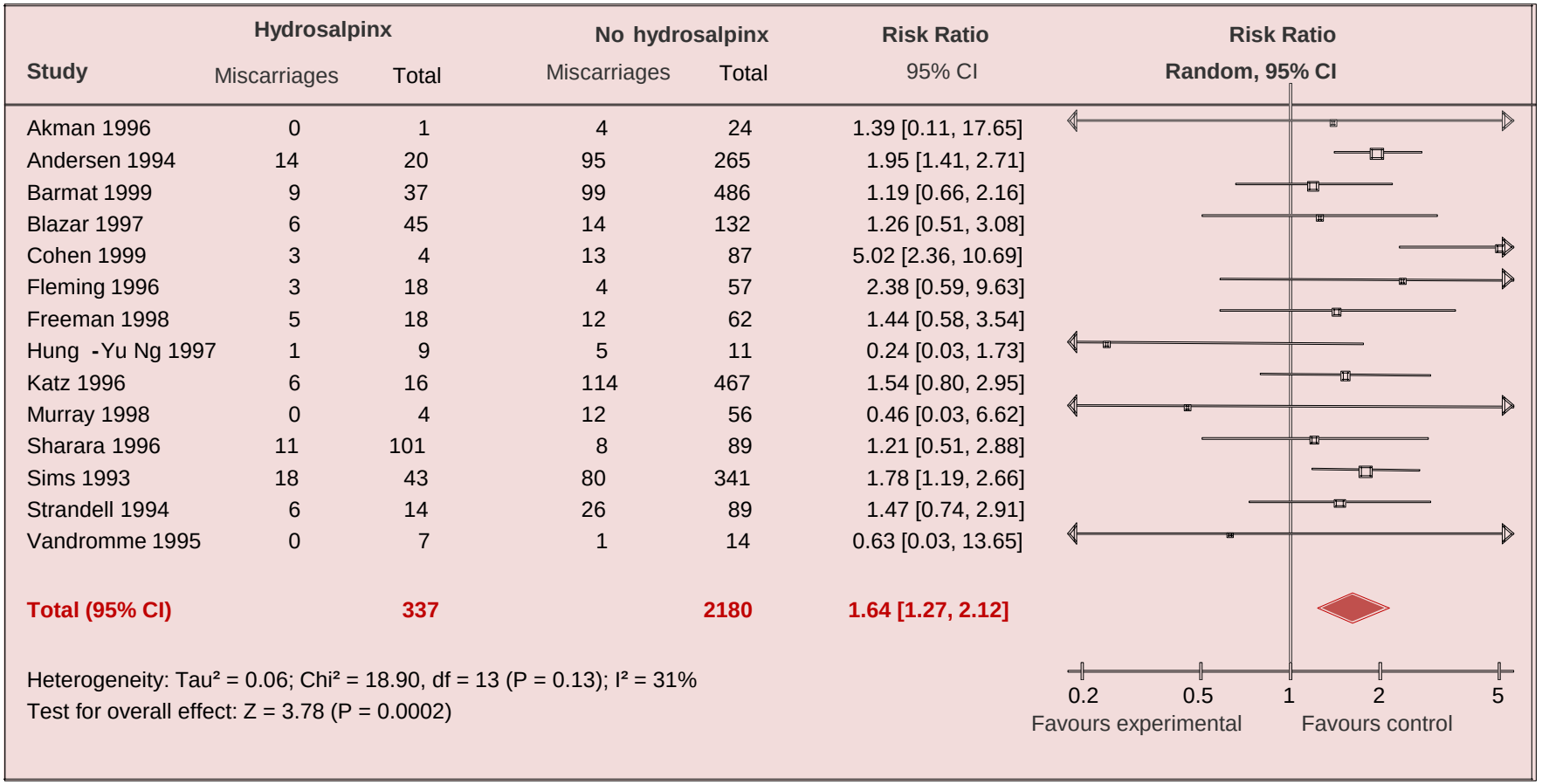


Figure 36. Meta-analysis of studies comparing miscarriage rate in women who had treatment (all interventions) for hydrosalpinx to women who did not undergo treatment for hydrosalpinx

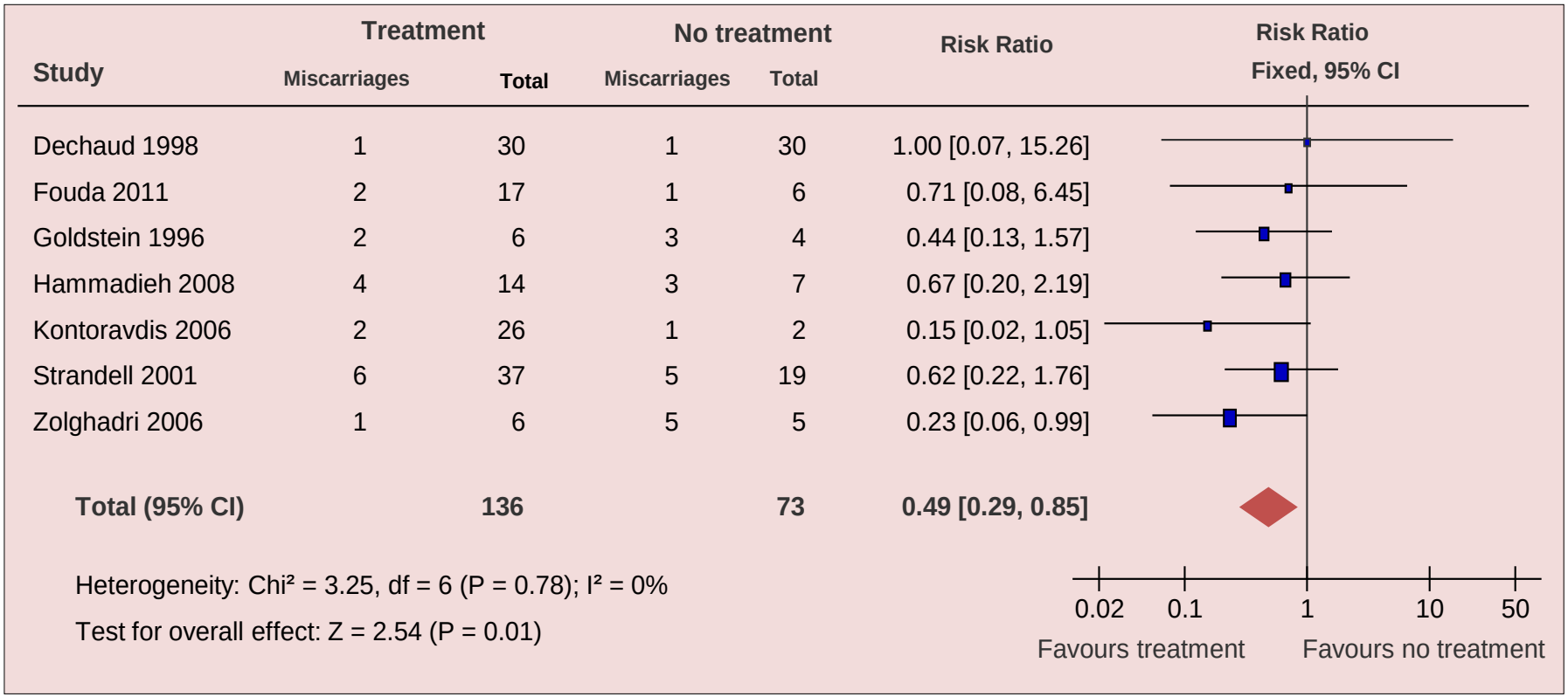


Figure 37. Meta-analysis of randomised studies comparing miscarriage rate in women who had salpingectomy for the treatment of hydrosalpinx to women who did not undergo treatment for hydrosalpinx

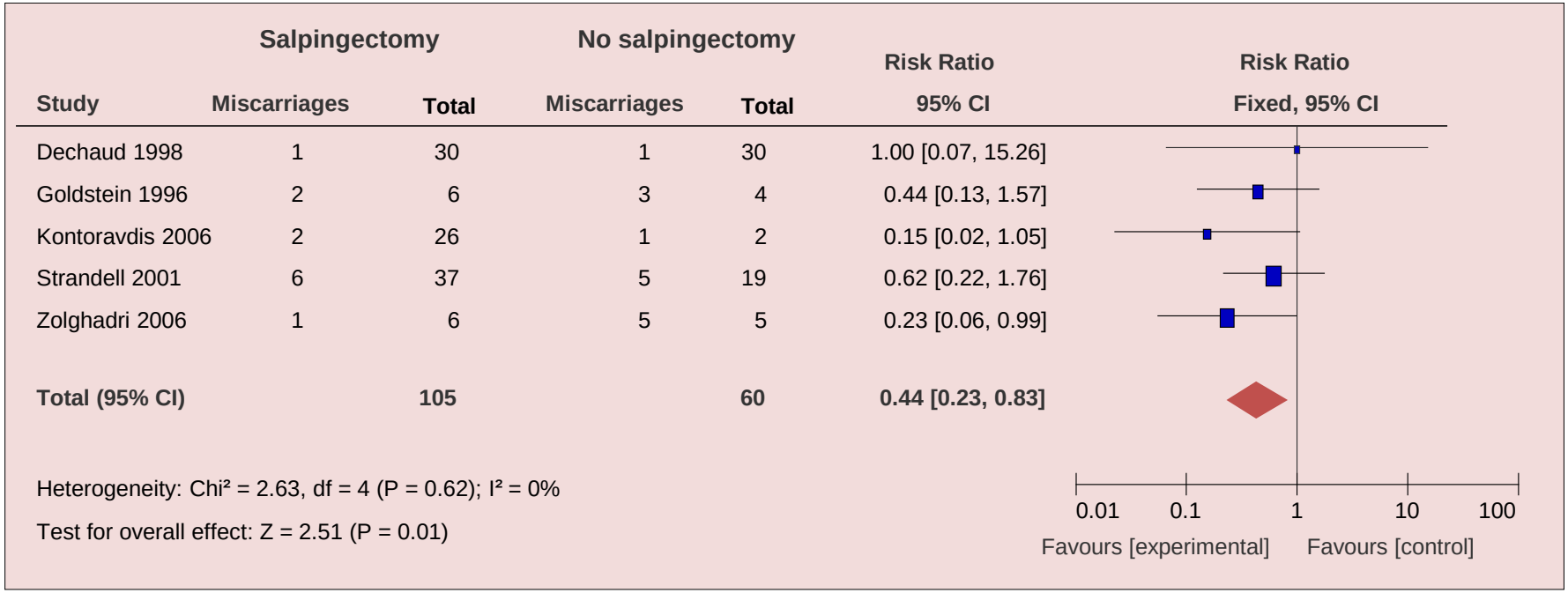


Figure 38. Meta-analysis of observational studies comparing miscarriage rate in women who had salpingectomy for the treatment of hydrosalpinx to women who did not undergo treatment for hydrosalpinx

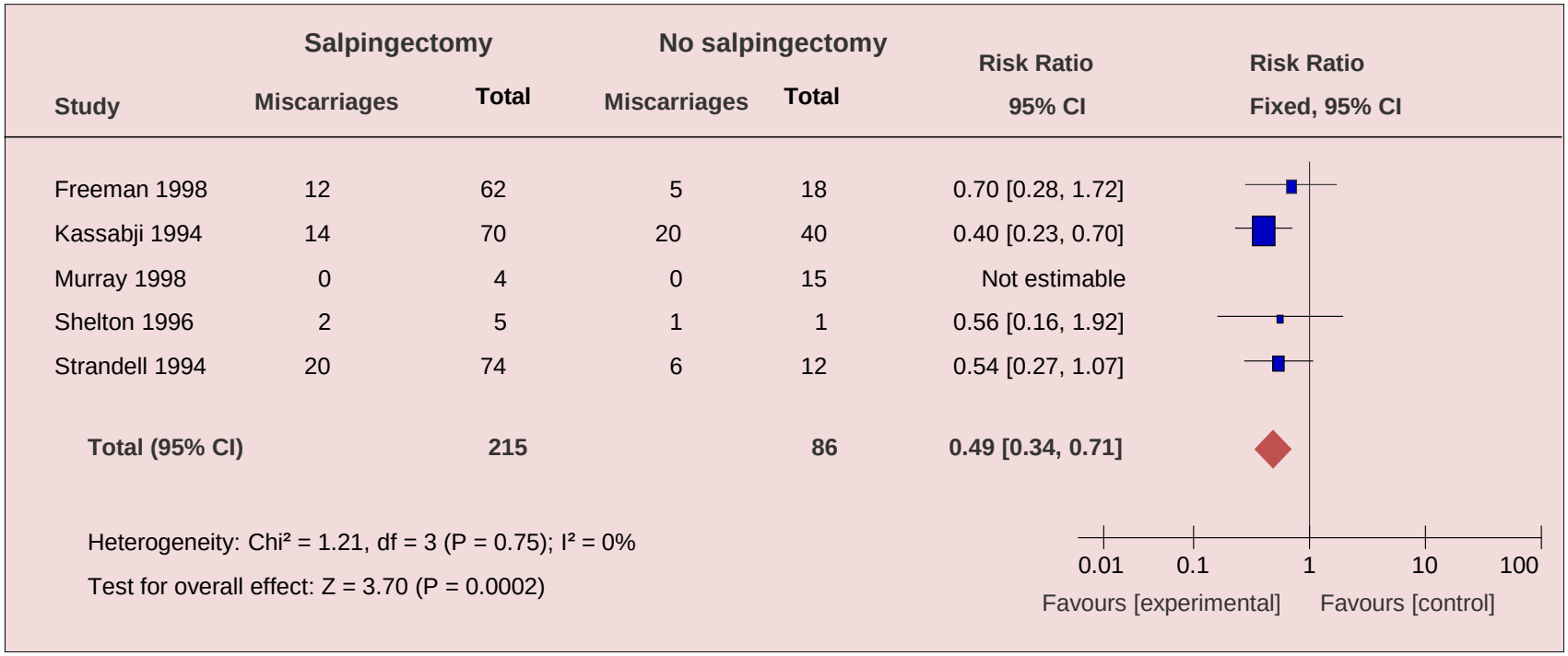
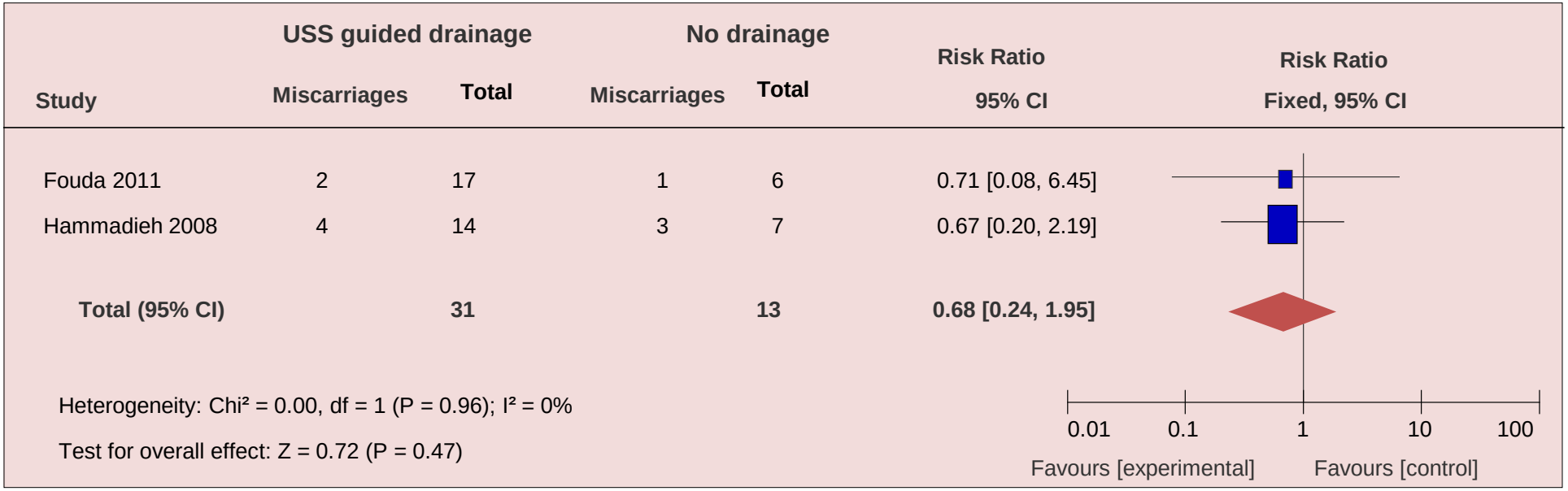


Figure 39. Meta-analysis of randomised studies comparing miscarriage rate in women who had ultrasound guided aspiration for the treatment of hydrosalpinx to women who did not undergo treatment for hydrosalpinx



DISCUSSION

This meta-analysis, which included 23 studies, found that the presence of hydrosalpinx is associated with an increased risk of miscarriage. Surgical treatment by salpingectomy can halve the risk of miscarriage in women with hydrosalpinx when compared to no treatment.

This review was strengthened by several factors. I performed an extensive search strategy and used valid data synthesis methods. I used the Cochrane and Newcastle-Ottawa quality assessment Scales to rate the quality of the included studies and the included studies scored well, suggesting low risk of bias. Furthermore, no language restrictions were applied.

Studies looking at miscarriage in women with hydrosalpinx following spontaneously conception were sparse with limited data, therefore all of the included studies were in pregnancies resulting from IVF/ICSI treatment. There was significant clinical heterogeneity between studies which differed in the diagnostic methods used to confirm the presence of hydrosalpinx; in some studies ultrasonography was used whilst others confirmed diagnosis by hysterosalpingography or on diagnostic laparoscopy. Whether all hydrosalpinges result in adverse outcomes or are only limited to those that are larger and visible with transvaginal ultrasonography remains uncertain (4). Furthermore, authors did not consistently report disease severity and whether included women had unilateral or bilateral tubal pathology. It is possible that women with bilateral disease may have had worse outcome than

those with unilateral disease. Similarly, disease severity could have had more adverse effect on a developing pregnancy and a potentially higher miscarriage rates would have been observed in this group. It was therefore not possible to analyse according to disease severity and the effect of unilateral versus bilateral disease could not be taken into account.

Miscarriage occurs most often due to chromosomal anomalies. The proportion of miscarriages due to chromosomal abnormalities varies dramatically with maternal age. Under the age of 35 years, 36% of miscarriages are due to trisomies; between 35 and 39 years, the rate rises to 46%, and > 40 years of age, trisomies are associated with 70% of miscarriages. (108) A more recent study (109) confirmed these findings, with an aneuploidy rate of 34.8% in women aged < 35 years, and 45.7% in women aged ≥ 35 years. Therefore age is a strong confounding factor. The median age for the included women was 33, therefore the findings of this review are unlikely to have been significantly affected by this factor.

It is widely established that hydrosalpinx is associated with poor implantation and clinical pregnancy rate. (91;94;98;103;105;106) Moreover, it has been demonstrated that treatment for hydrosalpinx can improve pregnancy chances. (28;28;95;97) However, this review addresses the question of whether hydrosalpinx has a detrimental effect on an established pregnancy, and looks at the effect of treatment on miscarriage outcome.

This review found that the presence of hydrosalpinx is associated with a 64% relative increase in the risk of miscarriage when compared to women who do not have hydrosalpinx. The exact mechanisms behind the observed increase in miscarriage rate are not yet well understood. Hydrosalpinx fluid is known to be embryotoxic and contains growth factor inhibitors. Moreover, it has been suggested that hydrosalpinx fluid contains lower levels of proteins and bicarbonate than does serum and may also contain cellular or infectious debris, lymphocytes, and other components, such as cytokines, prostaglandins, leukotrienes and catecholamines (7), all of which may have deleterious inflammatory, infectious, or immunological effects on the developing embryo(10) and can make the endometrium hostile to embryo development(6).

Another explanation is mechanical flushing of the implanted embryo, especially in patients with recurrent hydrorrhea. Moreover, endometrial blood flow is important for the continuation of an implanted pregnancy; one study (9) has investigated the blood flow in patients with and without hydrosalpinges and found that the endometrium and subendometrium of patients with hydrosalpinges have a significantly lower blood flow, compared with patients without hydrosalpinges.

This review has demonstrated that treatment for hydrosalpinx can reduce the risk of miscarriage. Meta-analysis of five randomised controlled trials found that when salpingectomy was performed, the risk of miscarriage was halved when compared to no treatment. Ultrasound guided aspiration of hydrosalpinges was performed in two trials of randomised trials which individually found a reduction in the miscarriage

rate, however the studies were small and meta-analysis did not reach statistical significance, leaving the need for more trials assessing aspiration of hydrosalpinges.

Recurrent miscarriage is defined as the loss of three or more consecutive pregnancies, and affects 1% of couples trying to conceive. Current RCOG guidelines do not routinely recommend tubal assessment as part of the investigations offered to women suffering from recurrent miscarriage. (20) It is possible that women with unilateral hydrosalpinx are suffering recurrent pregnancy loss and the findings of this review raise the question whether introducing screening for tubal pathology and treatment can reduce the risk of miscarriage in this population. This is further supported by a randomised controlled trial which assessed the benefit of unilateral proximal tubal fulguration in cases of unexplained early recurrent miscarriage. In this study, included women were those women screened for known causes of recurrent miscarriage and a diagnosis of unilateral hydrosalpinx by hysterosalpingography was the only positive finding. The study findings showed that pregnancy outcome in terms of early miscarriage improved significantly after proximal tubal fulguration of the tube affected by hydrosalpinx. Further research is needed to assess benefit of screening by hysterosalpingography in women affected by recurrent miscarriage.

To conclude, there is evidence to suggest that the presence of hydrosalpinx is associated with an increased risk of miscarriage. Treatment for hydrosalpinx can reduce the risk of miscarriage in these women.

CHAPTER 8

THE EFFECT OF ETHNICITY ON MISCARRIAGE: A COHORT STUDY AND META-ANALYSIS

Objectives

1. To explore the association between ethnicity and miscarriage
2. To identify at risk groups
3. To determine whether natural or assisted conception is associated with an increase in miscarriage risk in women of different ethnicity

ABSTRACT

Objectives

To investigate the association between ethnicity and miscarriage

Methods

A cohort study of all women undergoing their first IVF cycle at CARE (110) (*Centres for Assisted Reproduction*) clinic in the UK, with a systematic review and meta-analysis which incorporates the findings of the cohort study. For the cohort study, data were retrieved from 12 CARE (Centres for Assisted Reproduction) clinics from across the UK and Ireland, from 2008 to 2012. For the systematic review MEDLINE, EMBASE and CINAHL databases (inception – October 2014) were searched electronically. Studies were included where women underwent their first non-donor cycle of IVF (including intracytoplasmic sperm injection [ICSI] cycles). The primary outcome was miscarriage; secondary outcome was clinical pregnancy.

Results

For the cohort study a total of 5110 clinical pregnancies were analysed. The ethnic groups were; White (3970), Black (48), Asian (409), Chinese (27), Mixed (175), Other (48) and Not stated (591). 15 observational studies were included in the systematic review, of which 5 studies were in naturally conceived pregnancies and 10 studies in the IVF population. Quality assessment of the studies in the meta-analysis showed a low risk of bias.

In the cohort study, women of Asian ethnicity were found to have an increased miscarriage risk when compared with White women (OR 1.63 [1.05-2.54] p=0.03) after adjusting for age, BMI, previous live birth, previous miscarriage.

The meta-analysis found a statistically significant increase in miscarriage in women of Black ethnicity when compared with White women (RR 2.15 [1.07-4.34] p=0.03) in naturally conceived pregnancies. Incorporating the findings of the cohort study, a similar finding in IVF pregnancies was observed showing an increased risk of miscarriage in Black women when compared to White women (RR 1.50 [1.42-1.57] p< 0.00001). Furthermore, women of Asian ethnicity undergoing IVF had an increased risk of miscarriage than their White counterparts (RR 1.37 [CI 1.10-1.71] p=0.007), however this finding was not demonstrated in naturally conceived pregnancies (RR 0.78 [0.26-2.29] p=0.65).

Conclusions

The results of both the cohort study and the meta-analysis strongly suggest that ethnicity has an effect on miscarriage risk. Black and Asian women have an increased risk of miscarriage when compared to White women, and this difference is not explained by the commonly known confounders. Further research is needed to understand the reasons for the observed difference and to allow a targeted approach to investigations and management.

This chapter is divided into two sections:

1- Observational study of miscarriage in women undergoing their first non-donor cycle of IVF/ICSI treatment
2- Systematic review and meta-analysis of studies of ethnicity and miscarriage, incorporating the findings of the cohort study

COHORT STUDY

Methods

Study Design

This observational cohort study included all women undergoing their first non-donor cycle of IVF or Intra-cytoplasmic Sperm Injection (ICSI) at Centres for Assisted Reproduction (CARE) clinic in the UK, from 2008 to 2012. CARE is the UK's largest independent provider of fertility services.

Data were obtained from 5 main fertility clinics within the CARE consortium; London, Nottingham, Manchester, Northampton and Sheffield and a further 7 nationally spread satellite centres; Bolton, Boston, Derby, Leicester, Mansfield, Northampton and Peterborough.

Within the CARE database ethnicity is divided into 17 specific groups which we grouped into 7 broader categories; White (White British, White Irish, any other White), Asian (Indian, Pakistani, Bangladeshi, any other Asian background), Black (Black Caribbean, Black African, other Black), Chinese, Mixed (White and Black Carribean, White and Black African, White and Asian, any other mixed), any other and not stated.

Statistical analysis

Data were analysed using SPSS (ver. 21.0; SPSS Inc., Chicago). The baseline patient characteristics were described giving frequencies with percentages, or means with standard deviations, where appropriate. To estimate the independent contribution of ethnic group to miscarriage, regression and multiple logistic regression analyses were performed to calculate odds ratios and corresponding

95% confidence intervals. A stepwise technique was used for multiple logistic regression. Variables used within the model were age, body mass index, previous live birth and previous miscarriage.

Results

A total of 5110 clinical pregnancies (defined as the presence of a gestational sac or foetal pole on ultrasound scan) were reported between 2008 and 2012 at the CARE clinics in the UK. The ethnic groupings were as follows; White (3970), Black (48), Asian (409), Chinese (27), Mixed (175), Other (48) and Not stated (591). The crude miscarriage rates were as follows; White 9.5%, Black 12.5%, Asian 11%, Chinese 3.7%, Mixed 10.3%, Other 6.3% and not stated 8.3%.

Tables 14-17 display an overall description of the results including univariate and multivariate analysis.

Table 14. Baseline characteristics across each ethnic group

	White (n=3970)	**Black (n=48)**	**Asian (n=409)**	**Chinese (n=27)**	**Mixed (n=175)**	**Other (n=48)**	**Not stated (n=591)**
Age (in years)							
<35	2575 (64.9%)	36 (75%)	323 (79%)	16 (59.3%)	120 (68.6%)	29 (60.4%)	353 (59.7%)
35.1-40	1069 (26.9%)	7 (14.6%)	72 (17.6%)	9 (33.3%)	37 (21.1%)	18 (37.5%)	162 (27.4%)
40.1-45	263 (6.6%)	5 (10.4%)	12 (2.9%)	2 (7.4%)	15 (8.6%)	1 (2.1%)	52 (8.8%)
>45.1	63 (1.6%)	0	2 (0.5%)	0	3 (1.7%)	0	24 (4.1%)
Body mass index	(n=1962)	(n=23)	(n=198)	(n=17)	(n= 290)	(n=24)	(n=41)
>18.5	32 (1.6%)	1 (4.3%)	4 (2.0%)	0	16 (5.5%)	0	0
18.6-25	1178 (60.0%)	8 (34.8%)	110 (55.6%)	15 (88.2%)	160 (55.2%)	13 (54.2%)	30 (73.2%)
25.1-30	587 (29.9%)	9 (39.1%)	72 (36.4%)	1 (5.9%)	81 (27.9%)	11 (45.8%)	8 (19.5%)
30.1-35	152 (7.7%)	5 (21.7%)	10 (5.1%)	0	30 (10.3%)	0	2 (4.9%)
>35.1	13 (0.7%)	0	2 (1.0%)	1 (5.9%)	3 (1.0%)	0	1 (2.4%)
Cause of infertility							
Male factor	2315 (58.3%)	24 (52.1%)	222 (54.3%)	16 (59.3%)	117 (66.9%)	27 (56.3%)	222 (37.6%)
Tubal factor	589 (14.8%)	9 (18.8%)	49 (12.0%)	8 (29.6%)	26 (14.9%)	7 (14.6%)	82 (13.9%)
Anovulation	513 (12.9%)	4 (8.3%)	81 (19.8%)	2 (7.4%)	25 (14.3%)	6 (12.5%)	91 (15.4%)
Female other	1034 (26.0%)	14 (29.2%)	80 (19.6%)	2 (7.4%)	49 (28.0%)	7 (14.6%)	111 (18.8%)
Unexplained	1170 (29.5%)	19 (39.6%)	145 (35.5%)	9 (33.3%)	45 (25.7%)	18 (37.5%)	173 (29.3%)
Duration of infertility (years) Mean ±SD	2.6 ±2.0	2.6 ±1.4	3.4 ±2.7	2.1 ±1.1	2.5 ±2.3	3.4 ±2.2	4.4 ±3.0
Previous live birth	734 (18.5%)	1 (2.1%)	76 (18.6%)	3 (11.1%)	37 (21.1%)	5 (10.4%)	131 (22.2%)
Previous miscarriage	746 (18.8%)	10 (20.8%)	65 (15.9%)	2 (7.4%)	29 (16.6%)	8 (16.7%)	36 (6.1%)

Table 15. Cycle data

	White (n=3970)	Black (n=48)	Asian (n=409)	Chinese (n=27)	Mixed (n=175)	Other (n=48)	Not stated (n=591)
Treatment type							
IVF	1198 (30.2%)	17 (35.4%)	115 (28.1%)	11 (40.7%)	41 (23.4%)	14 (29.2%)	184 (31.1%)
ICSI	2208 (55.6%)	27 (56.3%)	238 (58.2%)	10 (37.0%)	100 (57.1%)	26 (54.2%)	273 (46.2%)
FET	641 (16.1%)	6 (12.5%)	65 (15.9%)	6 (22.2%)	37 (21.1%)	10 (20.8%)	146 (24.7%)

Table 16. Outcome data

	White (n=3970)	Black (n=48)	Asian (n=409)	Chinese (n=27)	Mixed (n=175)	Other (n=48)	Not stated (n=591)
Miscarriage rate	378 (9.5%)	6 (12.5%)	45 (11.0%)	1 (3.7%)	18 (10.3%)	3 (6.3%)	49 (8.3%)

Table 17. Univariate and multivariate analyses

Ethnic Group	No. of cycles	Univariate analysis		Multivariate analysis*	
		OR (95% CI)	***P value***	OR (95% CI)	***P value***
White	3980	Reference		Reference	
Asian	409	1.18 (0.85-1.63)	0.3	1.63 (1.05-2.54)	0.03
Black	48	1.36 (0.57-3.21)	0.5	1.56 (0.44-5.44)	0.5
Chinese	27	0.37 (0.05-2.70)	0.3	0.56 (0.07-4.28)	0.6
Mixed	175	1.09 (0.66-1.80)	0.7	1.05 (0.54-2.03)	0.8
Other	48	0.63 (0.20-2.05)	0.4	1.40 (0.41-4.81)	0.6
Not stated	591	0.86 (0.63-1.17)	0.3	1.27 (0.48-3.31)	0.6

*Adjusted for age, BMI, previous live birth, previous miscarriage

SYSTEMATIC REVIEW AND META-ANALYSIS

Methods

Identification of literature and study selection

The population for this review was women of different ethnic groups that were reported to have a miscarriage. The study cohort consisted of non-White women identified within a specific ethnic group who have had a miscarriage and the comparison was White women who have had a miscarriage. The outcome was miscarriage rate in each group. The following electronic databases were searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science (inception- October 2014). A search strategy was carried out based on the following key words and/or medical subject heading (MeSH) terminology: ethnicity, ethnic group, ethnic, racial aspects, miscarriage, recurrent miscarriage, fetal death, abortion and embryo. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. No language restrictions were placed in any of our searches or study selection.

I excluded studies that did not specify ethnicity of included women, including studies which have grouped women as 'non-White' without specifying their ethnic group. Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinised by two reviewers independently (HH and FR) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publication, the most

recent and complete versions were selected. Any disagreements about inclusion were resolved by consensus.

I completed the quality assessment with a second reviewer (FR). The Newcastle-Ottawa Quality Assessment was implemented for quality assessment of the included observational studies. This scale assesses eight components, including representativeness of the exposed cohort, selection of non-exposed cohort, ascertainment of exposure, outcome at start, comparability by design or analysis, outcome assessment, duration and adequacy of follow up . One star is awarded as maximum for all items except for comparability where a maximum of two stars can be awarded. I used an arbitrary score based on the assumption of equal weight of all items included in the Newcastle-Ottawa Scale. This was used to give a quantitative appraisal of overall quality of the individual studies. The score ranged from 0 to 9, with a score of either 0 or 1 for each item. From each study, outcome data were extracted in 2 x 2 tables by two reviewers HH and FR.

Statistical analysis

For the analysis of miscarriage rates I analysed data per total number of pregnancies for each ethnic group (Caucasian, Black, Asian and Hispanic). Data for spontaneously conceived pregnancies was analysed separately from pregnancies achieved by assisted reproductive techniques (IVF/ICSI). I carried out statistical analyses using the Review Manager software (RevMan 5.3). Relative risks with 95% confidence intervals from each study were combined for meta-analysis using the Peto-modified Mantel-Haenszel method. The fixed-effect model for combining

data was used where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where clinical heterogeneity was deemed significant to expect that the underlying treatment effects differ between trials, or where I detected substantial statistical heterogeneity, I used random-effects meta-analysis to produce an overall summary of an average treatment effect across trials.

Heterogeneity was assessed graphically using forest plot and statistically using chi-squared test. To detect publication and related biases, I undertook funnel plot analysis using Egger's tests to evaluate for asymmetry.

Data extraction

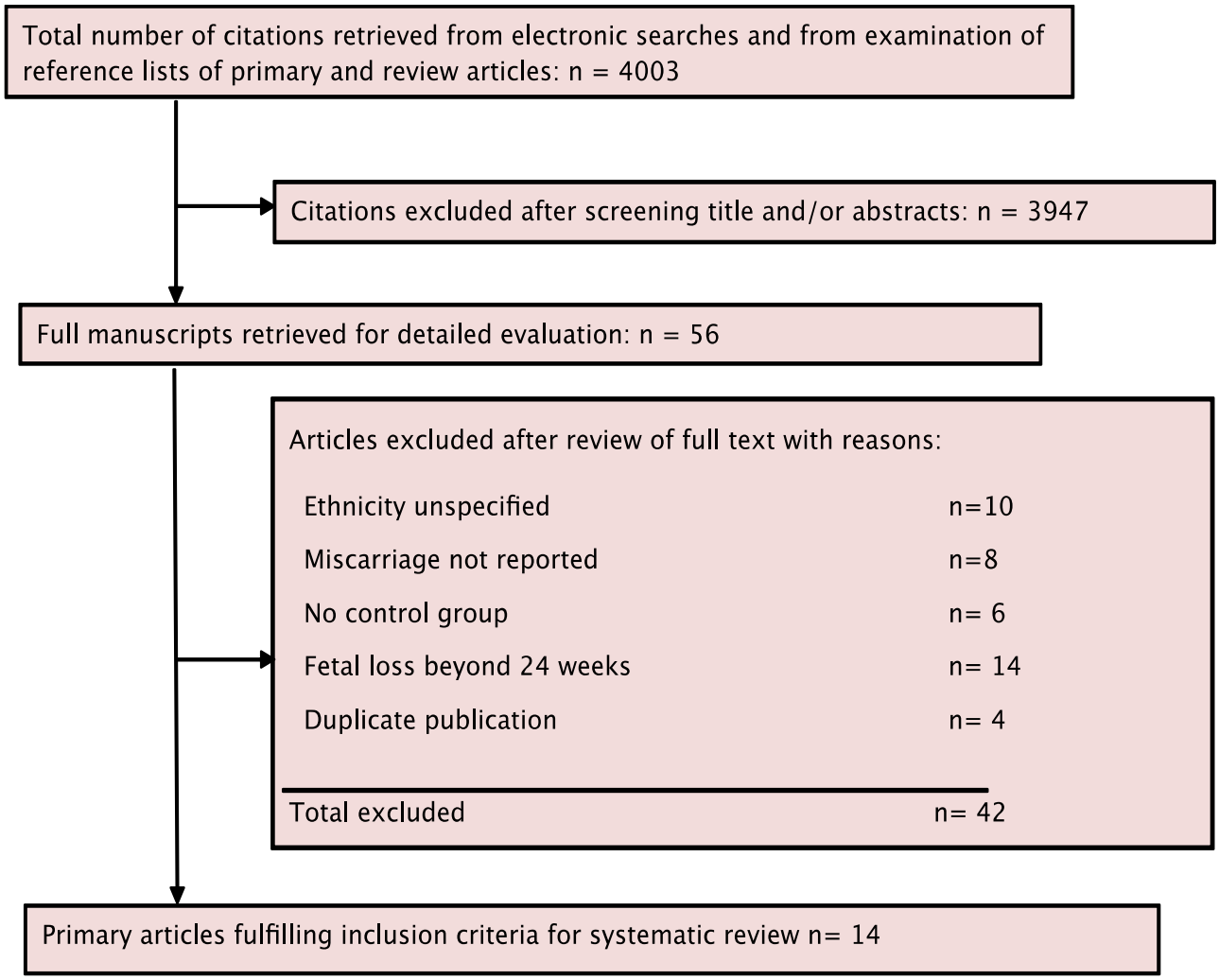
I designed a data extraction form to extract relevant data. A second reviewer (FR) extracted data using the agreed form. Any discrepancies were resolved by discussion.

Literature identification

The search strategy yielded 4003 citations (Figure 40) of which 3947 publications were excluded because it was clear from the title or abstract that they did not fulfil the selection criteria. I obtained full manuscripts for the remaining 56 articles. 42 publications were excluded because 10 did not specify ethnicity, 8 did not report miscarriage rate, 6 did not have a control group, 14 reported pregnancy loss beyond 24 weeks gestation, and 4 presented duplicate data. Therefore the total number of

studies included in the review was 14 (111-124). All of the included studies were of observational study design.

Figure 40. Study selection process for the systematic review of ethnicity and miscarriage



Study characteristics

The characteristics of the studies are presented in Tables 19 and 20.

Quality assessment

The Newcastle-Ottawa scale for Quality Assessment is presented in Table 18. The studies scored well on the scale. There was no evidence of publication bias on funnel-plot assessment.

Results

Naturally conceived pregnancies

Black vs Caucasian

Pooling of results from 5 studies that reported miscarriage as an outcome found an increased risk of miscarriage in Black women when compared with White women (RR 2.15 [1.07-4.34] p=0.03, Figure 41). There was significant variation across studies as indicated by an I^2 value of 98% ($p < 0.00001$).

Asian vs Caucasian

Pooling of results from 3 studies that reported miscarriage as an outcome showed no difference in the risk of miscarriage in women of Asian ethnicity when compared to women of White ethnicity (RR 0.78 [0.26-2.29] p=0.65, Figure 42). There was moderate heterogeneity across studies as indicated by an I^2 value of 49% (p=0.14).

Table 18. Appraisal of methodological quality (Newcastle-Ottawa Scale) of included studies

Study	Case-cohort representative	Selection of non-exposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design §	Comparability by analysis	Outcome assessment	Duration of follow-up	Score
Goetzl (2004)	*	*	*	*	**	*	*	*	9
Lyon (1994)	*	*	*	*	x	*	*	x	6
Hassan (2009)	*	*	*	*	**	*	*	*	9
Mukherjee (2012)	*	*	*	*	**	*	*	*	9
Seifer (2010)	*	*	*	*	**	*	*	*	9
Shahine (2009)	*	*	*	*	**	*	*	*	9
Sharara (2011)	*	*	*	*	*	*	*	*	8
Csokmay (2011)	*	*	*	*	*	*	*	*	8
Bendikson (2004)	*	*	*	*	*	*	*	*	8
Sharara (1999)	*	*	*	*	*	*	*	*	8
Palep-Singh (2006)	*	*	*	*	**	*	*	*	9
Mahmud (1995)	*	*	*	*	*	*	*	*	8
Wyatt (2005)	*	*	*	*	*	*	*	*	8
Feinberg (2006)	*	*	*	*	**	*	*	*	9

* - Indicates that feature is present; x- feature is absent. **§-** For comparability by design this checklist awards a maximum of two stars (**), one (*) or none if the feature is completely absent (x).

Table 19. Table of characteristics of studies of miscarriage in naturally conceived pregnancies

Study	Population	Ethnic groups	Outcome	Study design
Goetzl, 2004 **n=7932**	7932 pregnant women at 10 to 14 weeks gestation were recruited from 12 US and Canadian centres	African American = 344 Caucasian =6561 Hispanic =445 Asian =416 Other =160	Miscarriage Rate	Prospective cohort study
Lyon, 1994 **n=11046**	The outcome of 11,046 infant, from 20 weeks gestation, born to mothers of different ethnic origin within one London borough during the period from June 1990 to end of 1992	White = 8281 Asian = 1219 African = 597 West Indian = 949	Miscarriage Rate	Retrospective cohort study
Wyatt, 2005 **n=264,653**	Women undergoing routine screening for Down syndrome or neural tube defects between 1995 and 2000	White = 160, 567 Asian = 45, 723 Black = 13, 826	Miscarriage rate	Retrospective cohort study

Hasan, 2009 **n=3658**		White = 2458 Black = 767 Hispanic = 268 Other = 159 Unknown = 6	Miscarriage Rate	Prospective Cohort study
Mukherjee, 2013 **n=3533**	Women wishing to conceive and women in early pregnancy who were followed up till pregnancy outcome in the period from 2000 to 2009	White = 2732 Black = 801	Miscarriage Rate	Prospective cohort study

Table 20. Characteristics of studies of miscarriage in IVF pregnancies

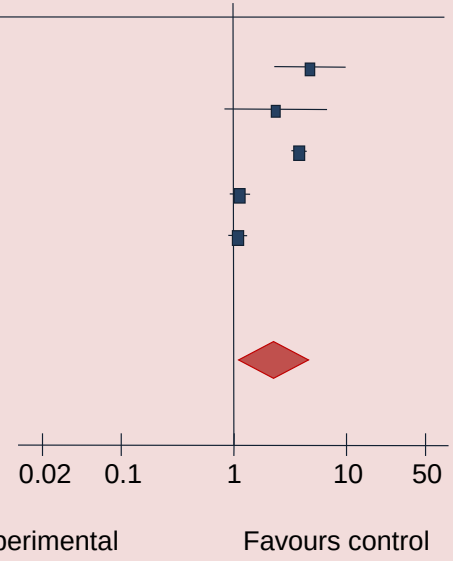
Author, year and study design	Sample population	Outcomes measured	Fresh/frozen cycles	Patient numbers
Csokmay et al 2011 **Retrospective Cohort Study**	All patients who underwent frozen blastocyst transfer between 2003 and 2008 in a University-based ART program. University of California at San Francisco	Miscarriage rate, clinical Pregnancy rate and Live birth rate	Frozen embryo cycles with autologous oocytes	Total 169 women Caucasian = 119 African American = 50
Seifer et al 2010 **Retrospective Cohort Study**	Non-donor IVF cycles between 2004 and 2006 in White and Black women, identified using the SART database (USA)	Miscarriage rate, Live birth rate per cycle started	Fresh and frozen non-donor IVF cycles	Total 158,693 cycles. Fresh cycles: Black = 10,354 White = 120,994 Frozen cycles: Black = 1,933 White = 25,412
Sharara et al 2000 **Retrospective Cohort Study**	Women undergoing IVF at an inner city, university-based IVF programme (University of Maryland, USA) between April 1997 and July 1999 and under the age of 40	Miscarriage rate, Implantation rate, clinical pregnancy rate and ongoing/delivered pregnancy rate	Fresh non-donor IVF cycles	Total 168 cycles White = 121 cycles Black = 47 cycles

Sharara et al 2012 **Retrospective Cohort Study**	All white and South Asian Women <40years undergoing blastocyst transfers at Virginia Centre for Reproductive Medicine, USA.	Miscarriage rate, Clinical PR and live birth rate	Non-donor, initial fresh cycle, blastocyst transfer	Total = 292 White = 238 cycles South Asian = 54
Shahine et al 2009 **Retrospective Cohort Study**	Indian and Caucasian Women undergoing blastocyst transfer between Jan '05 – July '07 in Stanford University fertility centre, USA	Miscarriage rate, Live birth rate per cycle started	Initial Fresh cycle, blastocyst transfer	Total 225 women Caucasian = 145 Indian = 80
Bendikson et al 2005 **Retrospective Cohort study**	Women undergoing first IVF cycle between August 1994 and March 1998 at Boston IVF, Brigham Womens Hospital and Boston Reproductive Science Centre (USA)	Live birth rate, chemical and ectopic pregnancies, miscarriage rate	First cycle, fresh non-donor transfer	Total 1135 cycles White = 1039 African American = 43, Hispanic = 18 Asian = 35.

Palep-Singh, 2006	Women undergoing IVF/ICSI cycles between 2000 and 2004 at Leeds Teaching Hospitals, Leeds (UK)	Gonadotrophin dose, number of oocytes retrieved, miscarriage, ongoing clinical pregnancy	Fresh IVF or ICSI cycles	Total 608 cycles White = 420 Asian = 188
Mahmud, 1995	Women undergoing first IVF cycles between April 1987 and December 1993 at Oxford Radcliffe Hospital, Oxford (UK)	Clinical pregnancy, miscarriage, live birth rate	First IVF or ICSI cycles	Total 132 cycles White = 88 Asian = 44
Feinberg, 2006	Women undergoing first cycle of fresh, non-donor ART from 1999 to 2003 Within the DoD population, USA	Implantation, clinical pregnancy, miscarriage, live birth rate	First cycle of fresh, non-donor IVF or ICSI	Total 1227 cycles White = 974 Black = 273

Figure 41. Meta-analysis of studies comparing miscarriage risk in Black and White women in naturally conceived pregnancies

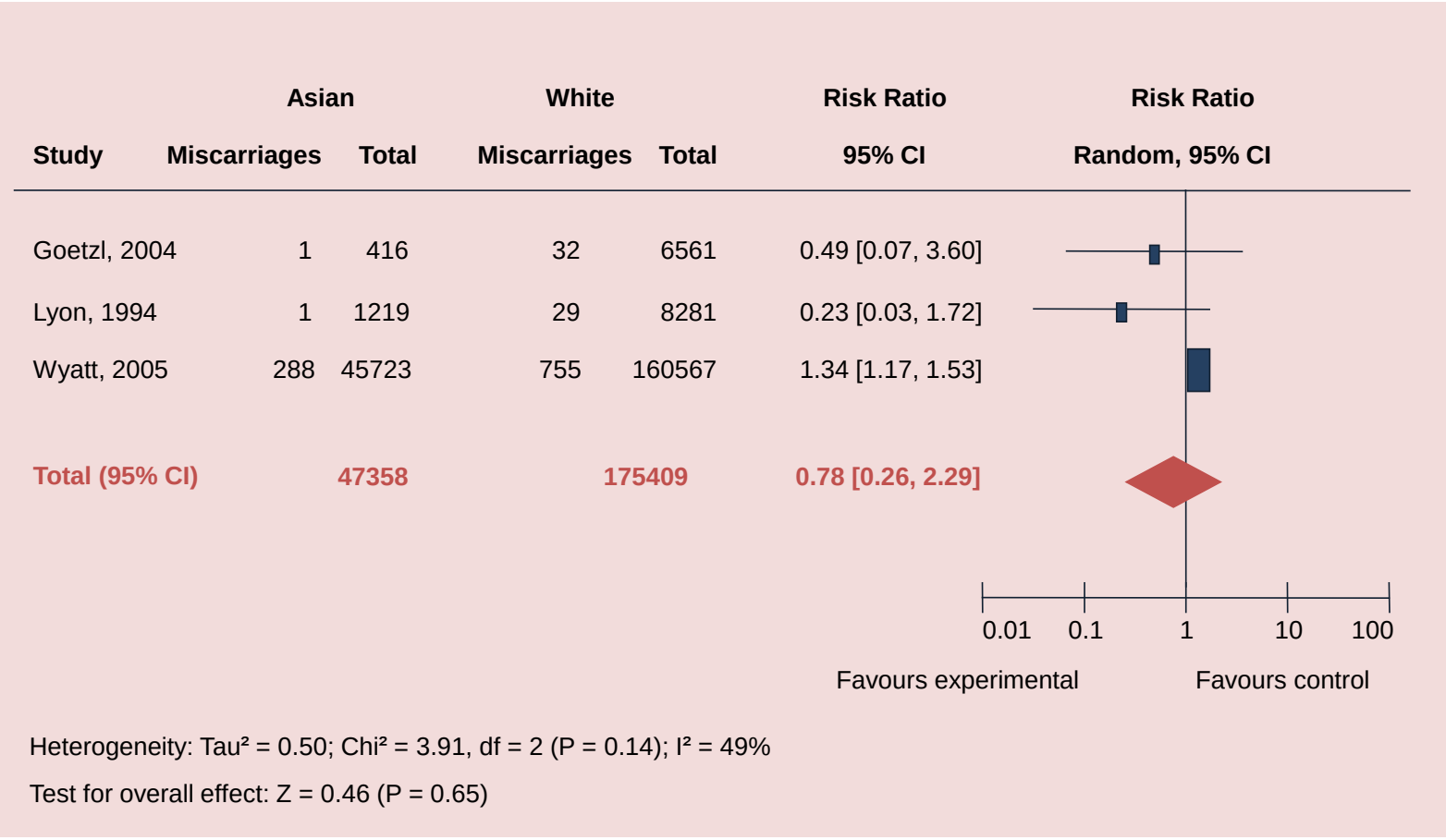
Study	Black Miscarriages	Total	White Miscarriages	Total	Risk Ratio Random, 95% CI
Lyon, 1994	10	597	29	8281	4.78 [2.34, 9.77]
Goetzl, 2004	4	344	32	6561	2.38 [0.85, 6.70]
Wyatt, 2005	249	13826	755	160567	3.83 [3.32, 4.42]
Hasan, 2009	124	767	347	2458	1.15 [0.95, 1.38]
Mukherjee, 2013	131	801	406	2732	1.10 [0.92, 1.32]
Total (95% CI)		**16335**		**180599**	**2.15 [1.07, 4.34]**



Heterogeneity: Tau² = 0.57; Chi² = 164.70, df = 4 (P < 0.00001); I² = 98%

Test for overall effect: Z = 2.15 (P = 0.03)

Figure 42. Meta-analysis of studies comparing miscarriage risk in Asian and White women in naturally conceived pregnancies



IVF/ICSI pregnancies

Black vs Caucasian

Pooling of results from 6 studies that reported miscarriage as an outcome found an increased risk of miscarriage in women of Black ethnicity when compared to women of White ethnicity (RR 1.50 [1.42 - 1.57] p< 0.00001, Figure 43). There was consistency across studies as indicated by an I^2 value of 0% (p=0.92).

Asian vs Caucasian

Pooling of results from 6 studies that reported miscarriage as an outcome in the found an increase in miscarriage risk in women of Asian ethnicity when compared to women of White ethnicity (RR=1.37, 95% CI 1.10 – 1.71, *p*=0.007, Figure 44). There was consistency across studies as indicated by an I^2 value of 1% (*p*=0.41).

Figure 43. Meta-analysis of studies comparing miscarriage risk in Black and White women in IVF pregnancies

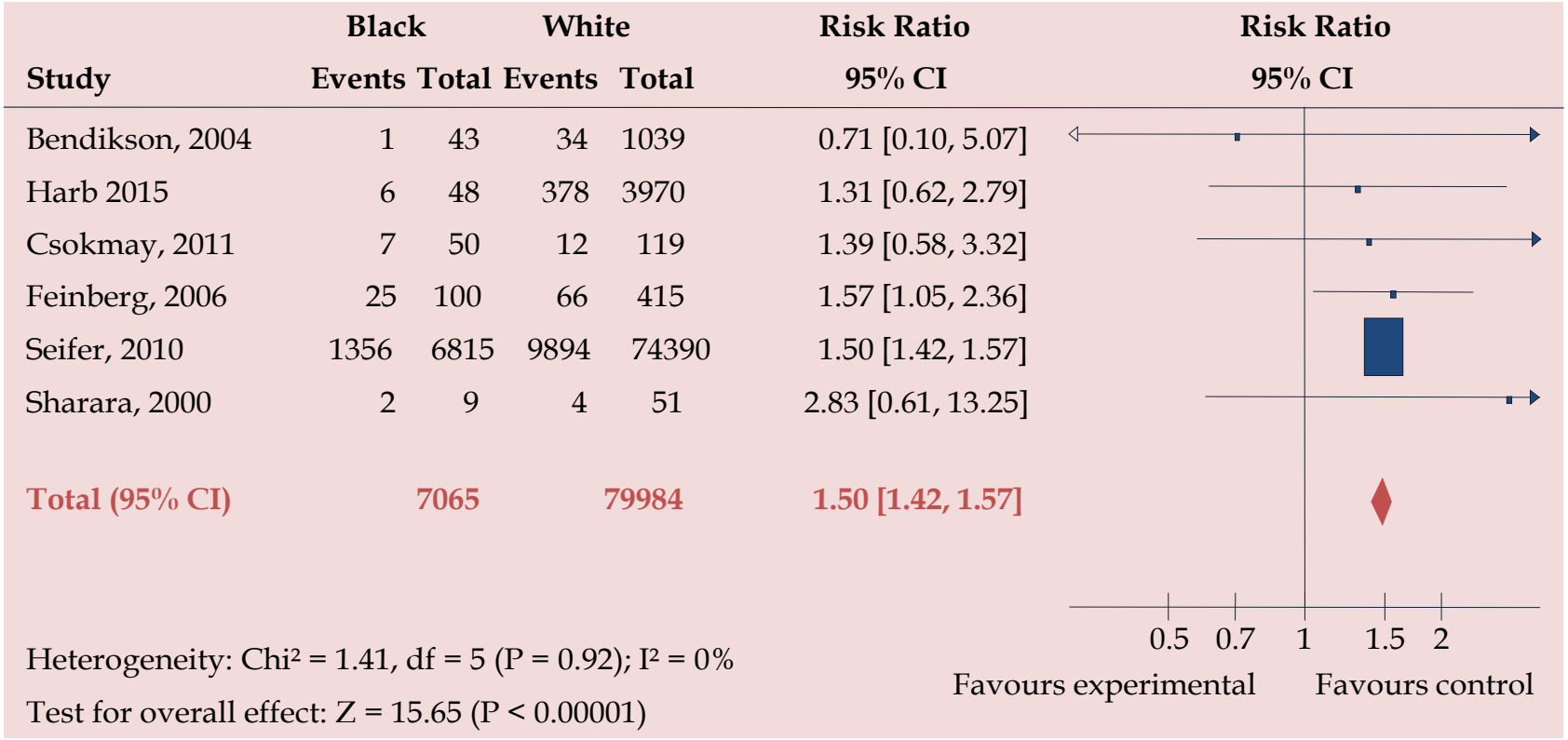
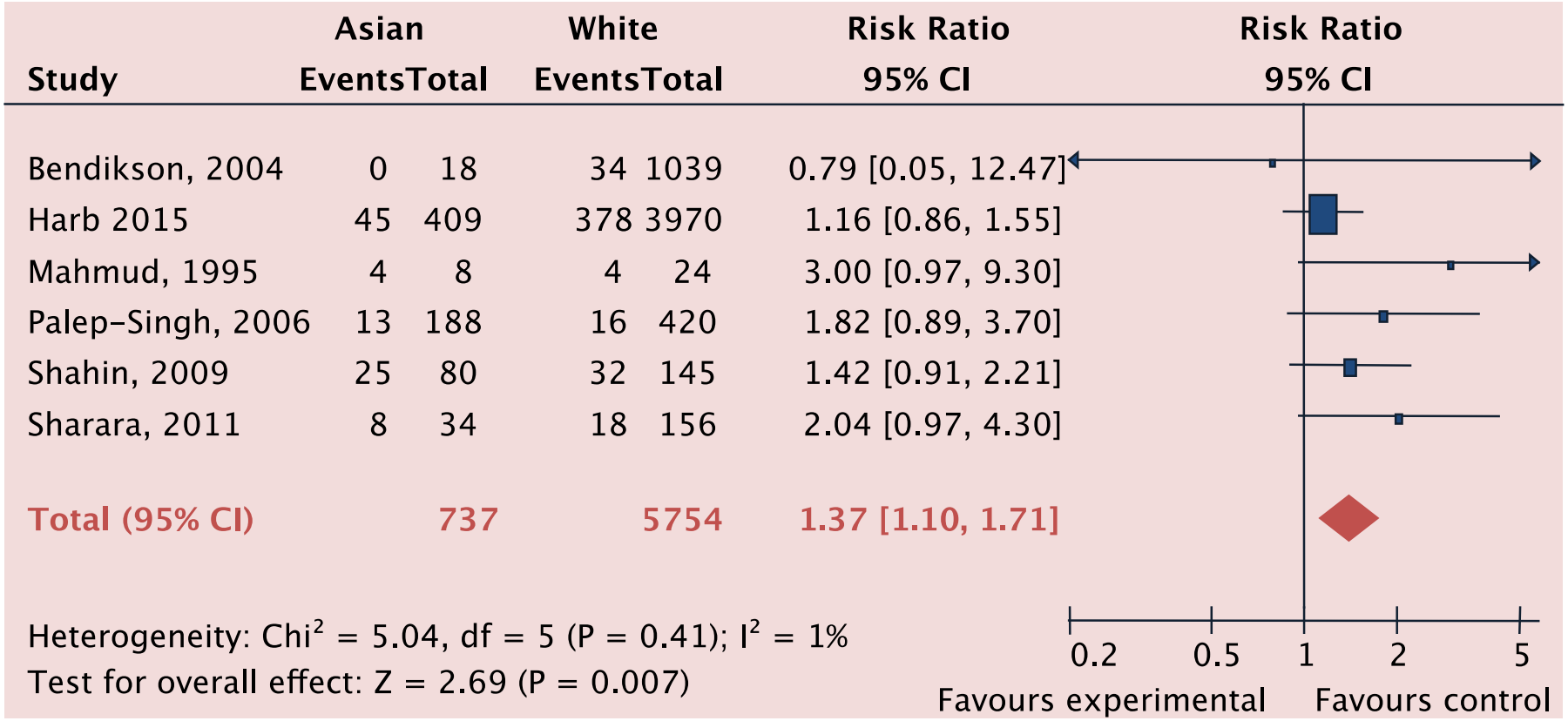


Figure 44. Meta-analysis of studies comparing miscarriage risk in Asian and White women in IVF pregnancies



Discussion

This systematic review found that women of Black ethnicity are at increased risk of miscarriage than White women in both naturally conceived and IVF pregnancies. Women of Asian ethnicity also have an increased risk of miscarriage in IVF pregnancies, however this finding was not demonstrated in naturally conceived pregnancies.

There are several factors that strengthen our analysis. We performed an extensive search strategy and used valid data synthesis methods. We used the Newcastle-Ottawa Quality Assessment Scale to rate the quality of the included studies and the included studies scored well on this scale, suggesting low risk of bias. Furthermore, no language restrictions were applied.

The findings of this review are limited by the number of included studies. Only 5 studies reported miscarriage risk for naturally conceived pregnancies in Black and White women, although they include a large sample size (n=196, 934). Similarly, 6 studies report miscarriage risk in Asian women (3 studies in spontaneous pregnancy and 3 studies in the IVF population) but have a large sample size (n=222,767 and 6491 respectively). Furthermore, studies did not consistently distinguish first from second trimester miscarriages. Several of the studies included all pregnancy losses below 24 weeks gestation. Miscarriages occurring in the second trimester of pregnancy are uncommon with a reported incidence of approximately 0.5% in low risk women (Westin et al, 2007). Moreover, it is possible

that variation exists within ethnic groups and the findings of this review may not be generalizable.

This review found that women of Black and Asian ethnicity appear to be at increased risk of miscarriage when compared to White women. A possible explanation for our findings is that women originating from certain ethnic groups are at more risk of having conditions which are associated with an increased risk of miscarriage. Firstly, uterine myoma are more prevalent in women of Black ethnicity, and tend to be multiple. (125;126) It is not known exactly how fibroids can cause miscarriage. The possible mechanisms are increased irritability of the uterus, mechanical compression by the fibroid and damage to the blood supply to the growing placenta or foetus. Intramural myomas have also been shown to be associated with a high rate of spontaneous miscarriage. Moreover, women who undergo uterine artery embolization (UAE) for the treatment of fibroids are reported to be at higher risk of miscarriage due to interruption to the endometrial blood flow. (127)

Secondly, diabetes mellitus and obesity is more prevalent in Black and Asian women than women of White ethnicity. (112) A four-fold increase in the risk of spontaneous miscarriage has been reported in diabetic pregnant women with poor glycaemic control in early pregnancy. (128) The risk of early miscarriage and recurrent miscarriage have been shown to be significantly higher among obese patients. (128-130) The exact reason for the obesity-related increased risk of miscarriage is not known. The possibility of oocyte abnormality was refuted by a

recent study of obese women receiving oocyte donation who experienced a higher rate of spontaneous miscarriage compared with normal weight peers. Undiagnosed pre-gestational diabetes may be linked with maternal obesity and increased miscarriage rate. (115) More interestingly some medical disorders that associated with increase miscarriage rate and pregnancy complications, like SLE, hypertension, and APS, are more prevalent, and even more severe in non-White, especially Black women, particularly in childbearing age, while auto-immune diseases are less prevalent in Hispanic and Asian women. (131)

Both sporadic and recurrent miscarriage are recognised complications of systemic lupus erythematosus (SLE). One study has found a 20% increase in the miscarriage risk in women with SLE. The presence of antiphospholipid antibodies (found in 1-3% of the healthy fertile population) whether primary or secondary to another condition such as systemic lupus, is associated with recurrent miscarriage. (20) Previous studies have shown that the prevalence and incidence of lupus is high in patients from certain ethnic groups including those of African descent in North America (Afro-Americans) or with a Caribbean background in the UK (Afro-Caribbeans), those of Asian descent including those from the Indian subcontinent (those from India or Pakistan, known as South Asians or Indo-Asians), those of Hispanic origin in North America, and those of Chinese background. (132-136)

The results of both the cohort study and the meta-analysis strongly suggest that ethnicity has an effect on miscarriage. Black and Asian women have an increased risk of miscarriage when compared with White women, and this difference is not

explained by the commonly known confounders. Further research is needed to understand the reasons for the observed difference to allow a targeted approach to investigations and management.

SECTION 3

INTERPRETATION AND CONCLUSION

CHAPTER 9

INTERPRETATION AND IMPLICATIONS FOR PRACTICE AND RESEARCH FOR CAESAREAN SCAR PREGNANCY

THE INCIDENCE AND MANAGEMENT OUTCOMES OF CAESAREAN SCAR PREGNANCY IN THE UK: A NATIONAL PROSPECTIVE COHORT STUDY

Chapter 5 presents a national prospective cohort study using the UK Early Pregnancy Surveillance Service to identify all women in the UK diagnosed with caesarean scar pregnancy over a 12 months surveillance period. No population-wide prospective incidence studies of caesarean scar pregnancy had been previously undertaken and the UK incidence was previously unknown.

The study found that the estimated UK incidence of CSP is 1 per 10 000 maternities [95% confidence interval (CI), 0.71 – 1.19]. This equates to one case every two years in a unit delivering 5000 women. Maternal age greater than 35 years, smoking, parity (2 or more) and number of previous caesarean section (2 or more) were strongly associated with an increased risk of having a caesarean scar pregnancy. These findings are important for the counselling of women who have had previous caesarean section delivery and who may wish to plan for further pregnancy. For the purpose of calculating the incidence of caesarean scar pregnancy, maternity data was used as the denominator population. A long term study of women who have had caesarean section delivery is recommended to allow a more accurate calculation of the true incidence of this condition.

The risk of CSP in a woman may be expected to increase with increasing number of previous caesarean sections , however this could not demonstrated in our study due to the limited sample size. Furthermore, it was not possible to determine

whether the indication for CS, the method for uterine closure (one vs two layers) and the choice of suture material are associated with risk of CSP as this information was poorly reported, often due to women delivering in another unit and their delivery details were not available to reporting clinicians. In this study, one woman (1/60, 1.6%) diagnosed with CSP was previously treated for caesarean scar pregnancy. Long term follow up of women with caesarean scar pregnancy is needed to identify the risk of recurrence.

Women should be fully counselled about all of the management options, including the benefits and risks associated with each treatment. The study found that the primary management most commonly used was surgical treatment, used in almost 2/3 of cases. Dilatation and curettage was performed in the majority of these cases. Methotrexate was administered in all women undergoing medical management. Interestingly, the study found that expectant management is chosen more often than medical management.

Women may choose to have expectant management for various reasons. Some women and clinicians may decide to watch and wait in the hope that the pregnancy will resolve spontaneously, which was the case in 4/10 women managed conservatively. Moreover in cases of diagnostic uncertainty conservative management may be more appropriate in the first instance. Some women may wish to preserve their pregnancy, whilst accepting the risks of maternal or fetal compromise. Indeed, four of the women in this study had a live birth following planned or emergency caesarean section; in all cases the women suffered massive

obstetric haemorrhage, necessitating an emergency hysterectomy in two women. Although most clinicians would probably prefer not to have to perform a caesarean section in a woman with a morbidly adherent placenta, ultimately it is the decision of the woman involved, and this should be respected. Regular antenatal visits, placental localisation during pregnancy and a plan for early delivery by caesarean section should be considered. Moreover, women should be cross matched prior to delivery, and it may be beneficial to involve a gynaecologist, vascular surgeon or interventional radiologist prior to, and preferably for them to be available at the time of delivery should emergency interventions for the control of haemorrhage be required.

Fifty percent of medically managed caesarean scar pregnancies were treated successfully with methotrexate. For women wishing to have less invasive treatment, this might be a suitable option however they should be informed of the risk of failure (50%), and the need for further treatment with repeat medical management or surgical management. This is because one of the main complications associated with medical management is retained products of conception.

Surgical treatment was the most commonly used treatment approach and is associated with the highest rate of successful treatment following primary management. This approach is associated with an increased risk of bleeding when compared with medical management, although this was not found to be statistically significantly.

We recommend that a shared management plan should be discussed and put in place early in pregnancy. The choice of treatment should be centred around the woman's preferences following full counselling on the treatment options.

CHAPTER 10

INTERPRETATION AND IMPLICATIONS FOR PRACTICE AND RESEARCH FOR SYSTEMATIC REVIEWS OF MISCARRIAGE STUDIES

Progesterone for threatened miscarriage

Chapter 6 presents a systematic review of progestogen use for threatened miscarriage. The findings of the review suggested that progestogens can reduce the risk of miscarriage by up to a half in women presenting with early pregnancy bleeding. The meta-analysis included seven studies which were small and of poor methodological quality.

To understand how the existing evidence is viewed by clinicians, I conducted UK and International Clinician surveys, as well as UK patient surveys.

The ***UK*** clinician survey (n=222) in Oct 2012 found that, in the UK, the vast majority of clinicians (212/222, 95.5%) do not use progesterone to prevent miscarriage in women with early pregnancy bleeding. The key reason for non-use is the lack of robust evidence. It is therefore not surprising that *the majority (201/222, 91%) called for a definitive trial*.

A survey of international practitioners was also conducted at FIGO (International Federation of Gynecology and Obstetrics) 2012 Conference, Rome. Surprisingly, this survey found the majority of clinicians (61/68, 90%) already use progesterone in women with early pregnancy bleeding, *although the vast majority (56/66, 85%) were willing to recruit into a randomised trial,* (Figure 38) presumably indicating lack of confidence in the available evidence.

UK patient survey

I conducted a survey to seek the opinion of women seen in the Early Pregnancy Unit (n=79) at Birmingham's Womens Hospital, in December 2012. The majority of women (57/79, 72%) said they would consider taking part in the trial, and 70% (55/79) found the vaginal route of administration acceptable. Furthermore, an independent survey was conducted by the Miscarriage Association to identify women's opinions on a double-blind placebo-controlled trial in early pregnancy and the acceptability of administering vaginal or rectal medications. The findings of this survey of 128 women showed that 91% (116/128) would enter or consider entering the trial. The vaginal route of administration of medicines was acceptable to 100/111 (90%) of women, and the rectal route acceptable to 91/111 (82%) of women.

Given the findings of my review, and the prioritisation of this important question by NICE, as well as the overwhelming support from national international clinicians, and patients, I applied for funding as a co-investigator from the Health Technology Assessment, NIHR to address this important question. I was successful in being awarded a £1.8 million grant to perform a randomised placebo-controlled trial (The **PRISM** Trial: **PR**ogesterone **I**n **S**pontaneous **M**iscarriage Trial).

PRISM

Progesterone In Spontaneous Miscarriage

Figure 45. PRISM Trial aims and objectives

Aim: To evaluate the effects of progesterone treatment to prevent miscarriage in women with early pregnancy bleeding.

Primary objective:

1. To test the hypothesis that in women presenting with vaginal bleeding in the first trimester, progesterone (400mg pessaries, twice daily), started as soon as possible after a scan has demonstrated a visible intrauterine gestation sac and continued to 16 completed weeks of gestation, compared with placebo, increases maternities with live births beyond 34 completed weeks by at least 5%.

Secondary objectives:

2. To test the hypothesis that progesterone improves other pregnancy and neonatal outcomes, including gestation at birth and survival at 28 days of neonatal life.

3. To test the hypothesis that progesterone, compared with placebo, is not associated with substantial adverse effects to the mother or the neonate, including chromosomal anomalies in the newborn.

4. To explore differential or subgroup effects of progesterone in prognostic subgroups, including age, fetal heart activity, gestation at presentation, amount of bleeding and body mass index.

THE EFFECT OF PRESENCE AND TREATMENT OF HYDROSALPINX ON MISCARRIAGE RISK

Chapter 7 presents a systematic review of 23 studies which found that the presence of hydrosalpinx increases the risk of miscarriage in women who have an intrauterine pregnancy. Meta-analysis showed a 64% relative increase in the risk of miscarriage in women with untreated hydrosalpinx. Furthermore, the review suggested that in women who underwent salpingectomy, the risk was decreased by 56%.

The findings of this review demonstrate a continued harmful effect even after successful implantation and an established intrauterine pregnancy is confirmed on ultrasonography. It would support the current approach of treating women with hydrosalpinx prior to commencing IVF treatment. Although individual studies found a reduction in miscarriage in women who underwent ultrasound guided aspiration of hydrosalpinx, meta-analysis did not shown an overall effect, probably due to the size and number of included studies. A large study to determine the benefit of the latter tube conserving treatment can offer additional options for women who do not wish to have tubal disconnection. Moreover, the benefit of alternative surgical management with salpingostomy for the treatment of hydrosalpinx needs further assessment.

Furthermore, the findings of this review also raise the question whether women who have recurrent miscarriage should be routinely screened for the presence of hydrosalpinx. Women who have unilateral hydrosalpinx may be at increased risk of miscarriage after spontaneous conception. Currently, tubal assessment is not

routinely performed. Further research is needed to determine the benefit of tubal assessment through the use hysterosalpingography.

THE EFFECT OF ETHNICITY ON MISCARRIAGE

Chapter 8 presents a cohort study and meta-analysis of pregnancy outcome in women of different ethnic backgrounds. The findings suggest that women of Black and Asian ethnicity are at increased risk of miscarriage when compared to women of White ethnicity. This was demonstrated in naturally conceived and IVF pregnancies in women of Black ethnicity, and was observed in Asian women conceived after IVF treatment.

The reasons for these findings are not fully understood. We accounted for some of the known risk factors associated with miscarriage, such as age and BMI, however a difference was still demonstrated. It is known that fibroids, diabetes and obesity are more prevalent in women of Black and Asian ethnicity, and they are associated with an increased risk of miscarriage. Women should receive pre-pregnancy counselling on the benefits of optimising diabetes control and weight loss. Furthermore, evidence suggests that submucosal fibroids reduce implantation rates and increase miscarriage risk, and it has therefore been recommended that these should be removed prior to IVF treatment. Moreover, it has been suggested that intramural fibroids which distort the uterine cavity should be removed to potentially improve IVF outcome.

There is a need to understand why some groups are at greater risk of miscarriage than others, to enable the identification of targeted investigations and management for women at greater risk of miscarriage. Further research to assess whether these differences are genetically induced or are caused by other variables such as nutrition is required. This can also help offer appropriate counseling to these women.

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APPENDIX

APPENDIX 1:

HTA FUNDING AWARD LETTER