

## ELECTIVE CAESAREAN SECTION IN LOW-RISK WOMEN AT TERM: CONSEQUENCES FOR MOTHER AND OFFSPRING





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## COLOPHON

Title:	Elective caesarean section in low-risk women at term: consequences for mother and offspring
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Other reported interests:	<p>Membership of a stakeholder group on which the results of this report could have an impact: Chantal Lecart (Belgian Group of Neonatologists – GBN-BVN)</p> <p>A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Wilfried Gyselaers (Limburg Clinical Research Program (LCRP) Universiteit Hasselt for research on pre-eclampsia)</p> <p>Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Katrien Beeckman (member of the Flemish Organisation of Midwives – VBOV); Pierre Maton (French-speaking Group of neonatologists ASBL 'cercle francophone des néonatalogistes')</p> <p>Other possible interests that could lead to a potential or actual conflict of interest: Malcolm Griffiths (holds and has held various roles in NICE (National Institute for Health and Care Excellence): Secondary care representative (and vice-chair), NICE Quality Standards Advisory Committee (2013-), Assessor Panel member, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre (2016-), Expert Adviser, Centre for Clinical Practice, NICE (2016-), NICE CG132 Caesarean section: guideline surveillance review participant (2016); RCOG (Royal College of Obstetricians &amp; Gynaecologists): Obstetric Assessor, Each Baby Counts project, RCOG (2016-); and, MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK): Obstetric Assessor, Confidential Enquiries into Maternal Deaths, MBRRACE-UK/RCOG (2013-); Regional Chair Confidential Enquiries into Maternal and Child Health (2008-2011), RCOG, Clinical Guidelines Committee (2009-2014; vice-chair 2011-2014), Chair NICE Guideline Development Group for Caesarean Section (2010-2012), Chair NICE Quality Standard Topic Expert Group for Caesarean Section (2012-2013), Chair East of England Regional Development Group for O&amp;G (2006-2013), NHS – Shared Decision Making – Birth after Caesarean section patient</p>



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Publication date:

08 November 2016

Domain:

Health Technology Assessment (HTA)

MeSH:

Cesarean section; Delivery, Obstetric; Elective Surgical Procedures; Mortality

NLM Classification:

WQ 415

Language:

English

Format:

Adobe® PDF™ (A4)

Legal depot:

D/2016/10.273/83

ISSN:

2466-6459

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How to refer to this document?

Stordeur S, Jonckheer P, Fairon N, de Laet C. Elective caesarean section in low-risk women at term: consequences for mother and offspring. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2016. KCE Reports 275. D/2016/10.273/83.

This document is available on the website of the Belgian Health Care Knowledge Centre.





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## LIST OF ABBREVIATIONS

<b>ABBREVIATION</b>	<b>DEFINITION</b>
aIRR	adjusted Incidence Rate Ratio
ADHD	Attention Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
ASQ	Ages and Stages Questionnaire
BMI	Body Mass Index
CD	Crohn Disease
CEpiP	Centre d'Épidémiologie Périnatale (Belgium)
CP	Cerebral Palsy
CS	Caesarean Section (delivery)
DVT	Deep Vein Thrombosis
EPDS	Edinburgh Postnatal Depression Scale
GA	Gestational Age
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
IPI	Inter Pregnancy Interval
IVD	Instrumental Vaginal Delivery
LOS	Length of stay
MA	Meta-Analysis
NICE	National Institute for Health and Care Excellence
PAHO	Pan American Health Organisation
PID	Pelvic Inflammatory Disease
RDS	Respiratory Distress Syndrome
OECD	Organisation for Economic Cooperation and Development
OR	Odds Ratio
RCT	Randomised Controlled Trial
RQ	Research Question
SDQ	Strengths and Difficulties Questionnaire
SPE	Studiecentrum voor Perinatale Epidemiologie (Belgium)



SR	Systematic Review
SVD	Spontaneous Vaginal Delivery
SUI	Stress Urinary Incontinence
TTN	Transient Tachypnea of the Newborn
UC	Ulcerative Colitis
UUI	Urgency Urinary Incontinence
VD	Vaginal Delivery
WHO	World Health Organisation



## ■ SCIENTIFIC REPORT

### 1 OBJECTIVES AND SCOPE

A caesarean delivery is a surgical procedure to deliver one or more babies. It can be performed when a normal vaginal delivery can be foreseen as too risky for the mother or the baby (elective caesarean section) or after attempted vaginal delivery when serious problems occur during labour (emergency caesarean section). However, there are growing concerns that some of the elective caesarean sections are performed '*on demand*' by the woman or the obstetrician, without real medical reason.<sup>1</sup>

In most countries, including Belgium, the rate of caesarean sections has steadily increased over the last decades. The previously recommended rate by the World Health Organisation in 1985 was a proportion of maximum 15% caesarean sections.<sup>2, 3</sup> This rate has been exceeded in most affluent countries.<sup>3</sup>

When medically justified, a caesarean section may be a good choice and can prevent maternal and perinatal mortality and morbidity. In low-risk pregnancies, caesarean sections for non-medical reasons may have negative short- and long-term effects for both the mother and the offspring.<sup>a</sup>

In this study, we performed a systematic literature search to compare the consequences for mother and the offspring of a caesarean section delivery (elective or emergency) versus a vaginal delivery (spontaneous, induced or assisted) in women with a low-risk pregnancy, insofar the literature allows to distinguish low-risk from high-risk pregnancies.

This report examines the clinical outcomes (physical and psychological) and does not include an economic analysis, an investigation of organisational aspects such as length of stay nor an ethical reflection. No assessment of the initiatives adopted in Belgium or in other countries to curb the growing trend of CS was undertaken. However, the importance of objective counselling on delivery modes will be discussed.

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<sup>a</sup> The term 'offspring' is used on purpose rather than 'child' since some studies report outcomes beyond the childhood period.



## 2 CAESAREAN SECTION

### 2.1 World Health Organisation recommendations

In 1985, the World Health Organisation (WHO) and the Pan-American Health Organisation (PAHO) held a shared conference on the appropriate technology for birth in Fortaleza, Brazil. Conclusions were published in the *Lancet*.<sup>2</sup> The optimal rate for caesarean section (CS) was considered by this international healthcare community to be between 10% and 15%.

In 2015, the WHO issued a statement on CS rates.<sup>3</sup> It starts from the observation that over the last 30 years CS rates gradually increased worldwide, both in developed and in developing countries. Many governments and clinicians expressed concern about the increased rates of CS deliveries and the potential negative consequences. In addition, the international community has referenced the need to revisit the 1985 recommended rate.

At a population level (ecological studies) increases in CS rates up to 10-15% are associated with decreases in maternal, neonatal and infant mortality. Above this level (and up to 30%), increasing the CS rate is no longer associated with reduced mortality. However, the association between higher rates of CS and lower mortality weakens or even disappears in studies that control for socioeconomic factors.<sup>3</sup>

In its statement the WHO concludes that there is no real optimal rate. But, rather than striving to achieve a specific rate every effort should be made to provide CS to women who really need it. It further concludes that CS is effective in saving maternal and infant lives, but only when it is required for medical reasons. To compare CS rates within healthcare facilities over time, between facilities and between countries a common classification system is needed. The WHO proposes using the Robson classification system (see 2.2) as a global standard for assessing, monitoring and comparing CS rates.<sup>3</sup>

### 2.2 Indications for caesarean section

In appropriate medical conditions and when performed properly, a CS can effectively prevent maternal and perinatal infant mortality and morbidity. But, increasingly, there is no medical indication for performing such a surgical procedure and CS is sometimes performed because of other concerns (e.g. hospital planning, the availability of obstetrician ensuing pregnancy, family organization at the time of birth (presence of spouse, care for other children) or the apprehension of labour-induced pain and risks of vaginal delivery fear of litigation etc.).

Many reasons to perform a CS are medically justified and clear indications are listed by medical experts. Those indications are often divided into absolute and relative indications. Absolute indications include situations such as (not an exhaustive list): absolute disproportion making vaginal delivery impossible, maternal pelvic deformity, fetal asphyxia or fetal acidosis, placenta praevia or uterine rupture. Relative indications include situations such as (non-limitative): failure to progress in labour (prolonged labour, secondary arrest) or previous CS.<sup>4</sup>

To rationalise indications for CS and to account for the specific case mix in a healthcare institution or at the national level a standardized tool was needed. The WHO proposed the universal use of the Robson classification, a tool developed by Dr Robson in 2001.<sup>1</sup>

The Robson classification divides CS into 10 mutually exclusive groups. It is now widely used in many countries.<sup>3</sup> This score classifies pregnancies from group 1: nulliparous with single cephalic pregnancy and  $\geq 37$  weeks gestation in spontaneous labour, to group 10: women with a single cephalic pregnancy  $< 37$  weeks gestation, including women with previous uterine scars.<sup>3</sup> It should be noted that this is not an ordinal scale (meaning the higher in the list does not mean it is also a higher risk) but just a classification system for comparison. The categories are easy to determine because they are based on five basic obstetric characteristics that are routinely collected in all maternities (see section 3.5 for more details on the Robson score). An advantage is that countries are allowed to supplement the Robson score with the subcategories they find important. In Canada, for example, the Robson classification was supplemented with several subcategories.<sup>5</sup>



Whereas no scientific evidence demonstrates the benefit of a CS for women or their offspring who do not require the procedure, a number of scientific publications report negative consequences of those unnecessary surgeries for maternal and offspring health.<sup>1, 3, 4</sup> Caesarean sections are suspected to be associated with short and long term risks which can occur many years beyond birth and could affect the health of the mother and her child, as well as future pregnancies.<sup>3</sup>

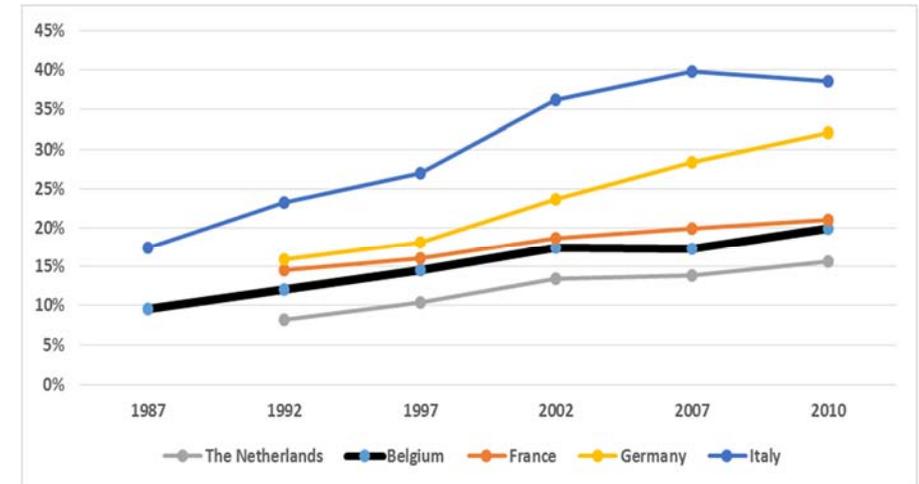
### 2.3 Caesarean section rates worldwide

Xie et al. (2015) published CS rates for 2010 for 31 high-income countries (the complete table can be found in the supplement [Appendix 1, Table 1]). In Europe, CS rates varied between 15.6% in the Netherlands and 50% in Greece.<sup>6</sup>

Changing rate over time were obtained from a study by Declercq et al. (2011) on CS rates between 1987 and 2007 in 22 industrialised countries using data from the WHO and the OECD.<sup>7</sup> In 2007, 11 of those countries reported overall CS rates of more than 25%, led by Italy (39%), Portugal (35%), the United States (32%), and Switzerland (32%) (Greece was not included in this overview). Five countries, the Slovak Republic, the Czech Republic, Ireland, Austria, and Hungary more than doubled their CS rates between 1992 and 2007. Comparing changes in rates across time periods, 14 countries experienced a greater increase in CS rates in the period between 1998 and 2002 compared with the period between 1993 and 1997. Comparing trends from 1998–2002 to 2003–2007, eighteen countries experienced a slowing down of the CS rate increase across these two periods (the complete table can be found in the supplement [Appendix 1, Table 2]).

The data, combining data from both sources for six selected European countries, are presented in Figure 1.

Figure 1 – Caesarean section rates in six selected European countries



Sources: Declercq et al.<sup>7</sup> (2011) for 1987 till 2007 and Xie et al.<sup>6</sup> (2015) for the 2010 data



## 3 BELGIAN SITUATION

### 3.1 Registration process

In Belgium, approximately 125 000 children are born each year. As shown in section 2.3, the CS rate in Belgium was around 20% in 2010, higher than in The Netherlands but much lower than in many other European countries such as Germany or Italy.

In Belgium, information on perinatal epidemiology is collected through the birth and death certificates. The quality management is performed by two centres (non-profit organisations), i.e. the 'Studiecentrum voor Perinatale Epidemiologie (SPE)' and the 'Centre d'Epidémiologie Périnatale (CEpiP)'.

The SPE's work covers all births in Flanders but also from one hospital in Brussels (the University Hospital of the VUB). Apparently, this institution is also included in the registration of the Brussels Region (Personal Communication V. Van Leeuw). This might lead to limited double counting of births.

The CEpiP's work covers all births in Wallonia and, separately, all births in the Brussel Region.

Both centres provide feedback and benchmarking data to the individual hospitals (anonymised except for the hospital concerned) to evaluate their practices on delivery methods.

The total number of babies born in 2014 was 129 114; this total was obtained by adding the numbers reported on in the three regional reports. However, the number of births for 2014 reported by Statistics Belgium (<http://statbel.fgov.be>) equalled only 124 415. Such a difference is not only due to double counting (see above) but also due to the exclusion of unregistered persons in the National Registry (while available in the CEpiP and SPE databases).

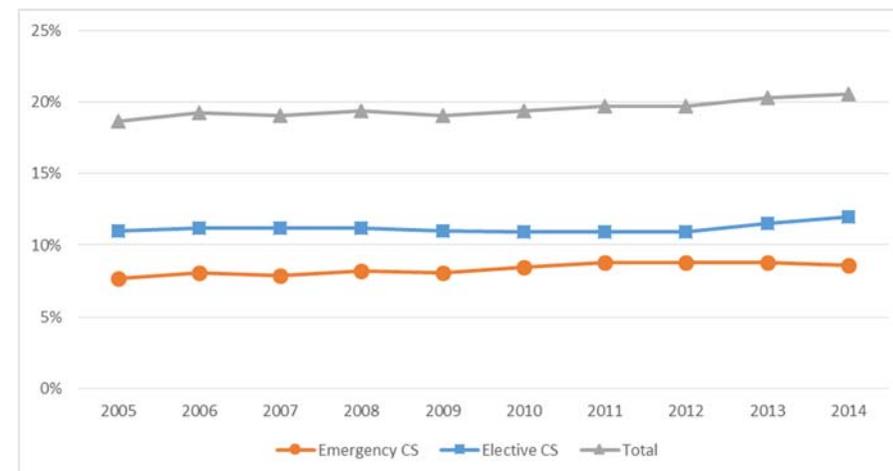
### 3.2 Flanders

Those data are based on the SPE year report for 2014.<sup>8</sup>

In 2014, 66 955 babies were born in Flanders. The proportion of CS in 2014 reached 20.6% (12.0% elective and 8.6% emergency CS). However, this proportion was much higher in multiple births compared to singletons: 56.4% vs. 19.9% respectively.

The CS rate is very different between maternities ranging from 11.8% to 29.1% (IMA data, 2014). Also in Flanders the proportion of CS is rising over the years, mainly due to an increasing proportion of elective CS. It is reported that by the start of the registration in 1987, the proportion of CS was 9.0%, in 1991 it was 10.9%. The evolution between 2005 and 2014 is shown in Figure 2.

Figure 2 – Evolution of CS rates in Flanders (2005 – 2014)



Source: SPE report (2014)<sup>8</sup>

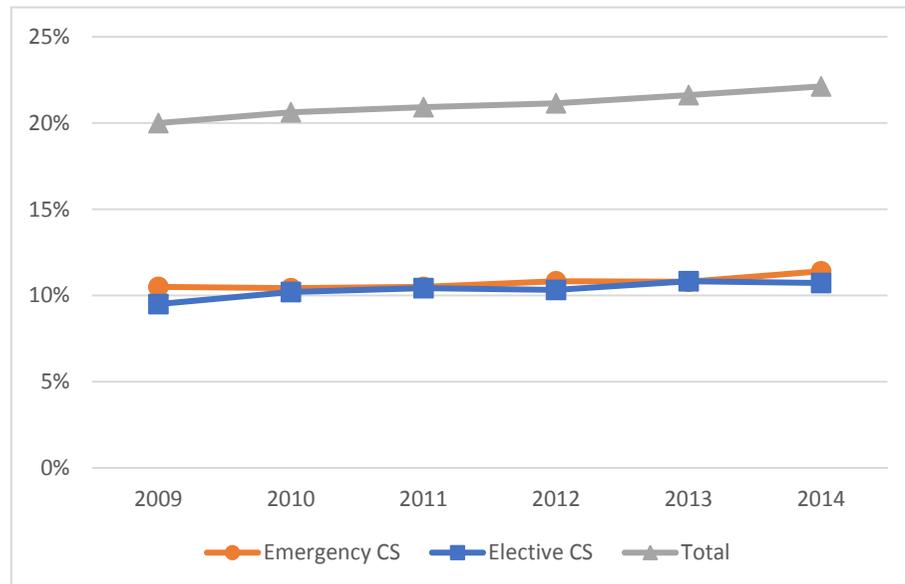


### 3.3 Wallonia

Those data are based on the CEpiP year report for 2014.<sup>9</sup> In 2014, 37 280 babies were born in Wallonia. The proportion of CS in 2014 reached 22.1% (10.7% elective and 11.4% emergency CS). However, this proportion was much higher in multiple births compared to singletons: 58.6% vs. 21.4% respectively.

The CS rate is very different between maternities ranging from 13.5% to 32.9% (IMA data, 2014). Also in Wallonia the proportion of CS is rising over recent years. Long-term data are limited in this report since the CEpiP only started recording data since 2008. However, even in the last six years a marked increase in the number of CS was observed as shown in Figure 3.

Figure 3 – Evolution of CS rates in Wallonia (2009 – 2014)



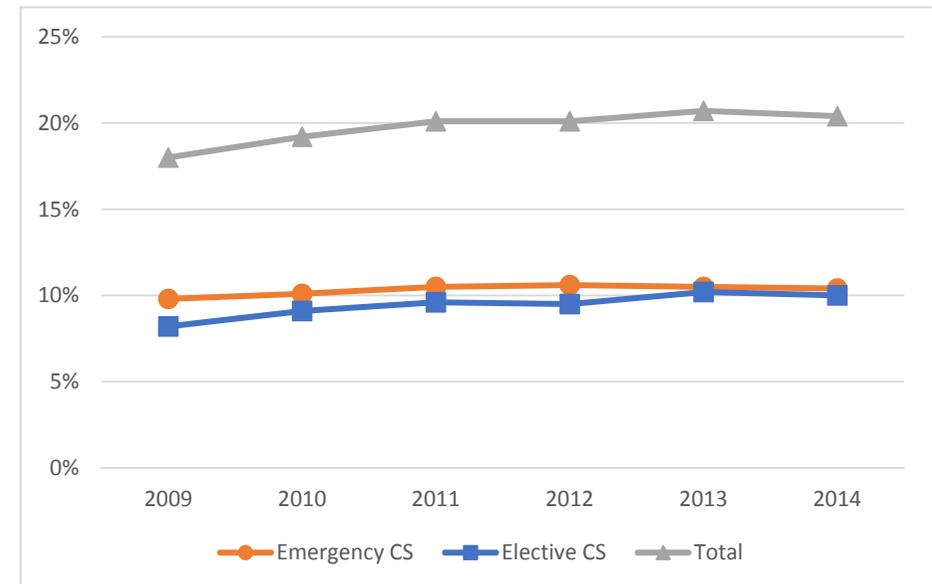
Source: CEpiP report (2014)<sup>9</sup>

### 3.4 The Brussels Region

Those data are based on the CEpiP year report for 2014.<sup>10</sup> In 2014, 24 879 babies were born in the Brussels Region. The proportion of CS in 2014 overall was 20.4% (10.0% elective and 10.4% emergency CS). However, this proportion was much higher in multiple births compared to singletons: 63.8% vs. 19.5% respectively.

The CS rate is very different between maternities ranging from 15.5% to 26.2% (IMA data, 2014). Also in Brussels the proportion of CS is rising over recent years. Long-term data are limited in that report since the CEpiP only started recording data since 2008. However, even in the last six years a marked increase in the number of CS was observed as shown in Figure 4.

Figure 4 – Evolution of CS rates in the Brussels Region (2009 – 2014)



Source: CEpiP report (2014)<sup>10</sup>



### 3.5 Comparing Belgian regions using the Robson classification

The Robson classification was designed to classify pregnancies and obstetrical information on clinically relevant items that are carefully defined and accurate, and that are collected timely and readily available.<sup>1, 3</sup>

All three regions in Belgium use the Robson classification to analyse use of CS. This classification uses ten mutually exclusive categories.

1. Nulliparous with single cephalic pregnancy,  $\geq 37$  weeks gestation in spontaneous labour
2. Nulliparous with single cephalic pregnancy,  $\geq 37$  weeks gestation who either had labour induced or were delivered by CS before labour
3. Multiparous without a previous uterine scar, with single cephalic pregnancy,  $\geq 37$  weeks gestation in spontaneous labour
4. Multiparous without a previous uterine scar, with single cephalic pregnancy,  $\geq 37$  weeks gestation who either had labour induced or were delivered by CS before labour
5. All multiparous with at least one previous uterine scar, with single cephalic pregnancy,  $\geq 37$  weeks gestation
6. All nulliparous women with a single breech pregnancy
7. All multiparous women with a single breech pregnancy including women with previous uterine scars
8. All women with multiple pregnancies including women with previous uterine scars
9. All women with a single pregnancy with a transverse or oblique lie, including women with previous uterine scars
10. All women with a single cephalic pregnancy,  $< 37$  weeks gestation, including women with previous scars

*Categories 2 and 4 will ideally be divided into a (inductions) and b (prelabour caesarean sections).*

The Robson classification is a simple and easy system to implement. The categories are based on relevant criteria, mutually exclusive and totally inclusive.

When comparing the three regions in Belgium there are few differences. Figure 5 shows the CS rate for each of the ten Robson categories among all deliveries. No major differences between regions are noted.

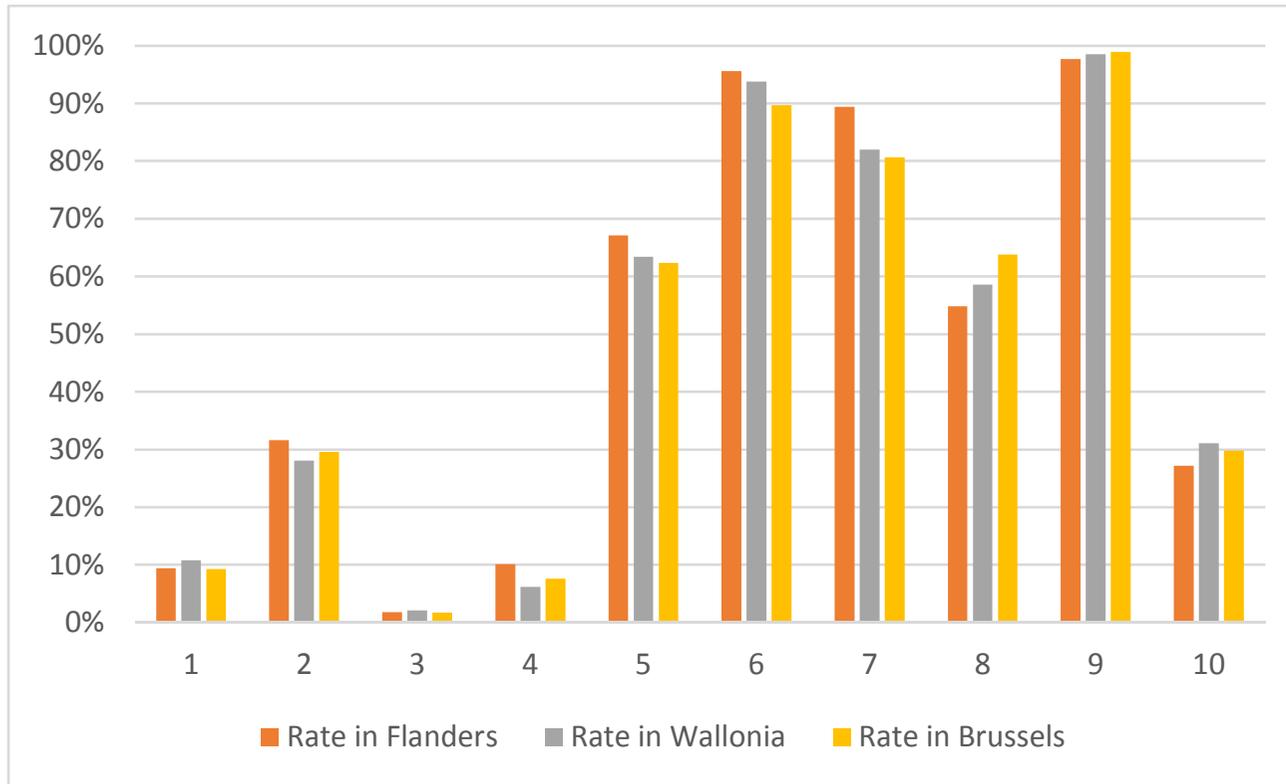
However, an increase of caesarean sections among primiparous women and multiparous women with at least one previous uterine scar is observed in the 2009-2013 period.<sup>8,10</sup>

Not all of those Robson categories are equally frequent. Therefore some of the groups contribute more than other categories to the total number of CS. Figure 6 shows the contribution of each category to the total proportion of caesarean sections performed. It is clear from this figure that all abnormal (transverse or oblique) lies, nulliparous/multiparous breeches and multiple pregnancies are mainly delivered by caesarean section. Globally, these four groups represent about 6% of all pregnancies and their contribution in the CS rates is relatively low (Figure 6).

The group 2 (nulliparous with single cephalic pregnancy,  $\geq 37$  weeks gestation who either had labour induced or were delivered by CS before labour) and the group 5 (women with previous CS, but with at-term single cephalic presentations) constitute the largest proportion of the CS deliveries in all Belgian regions.



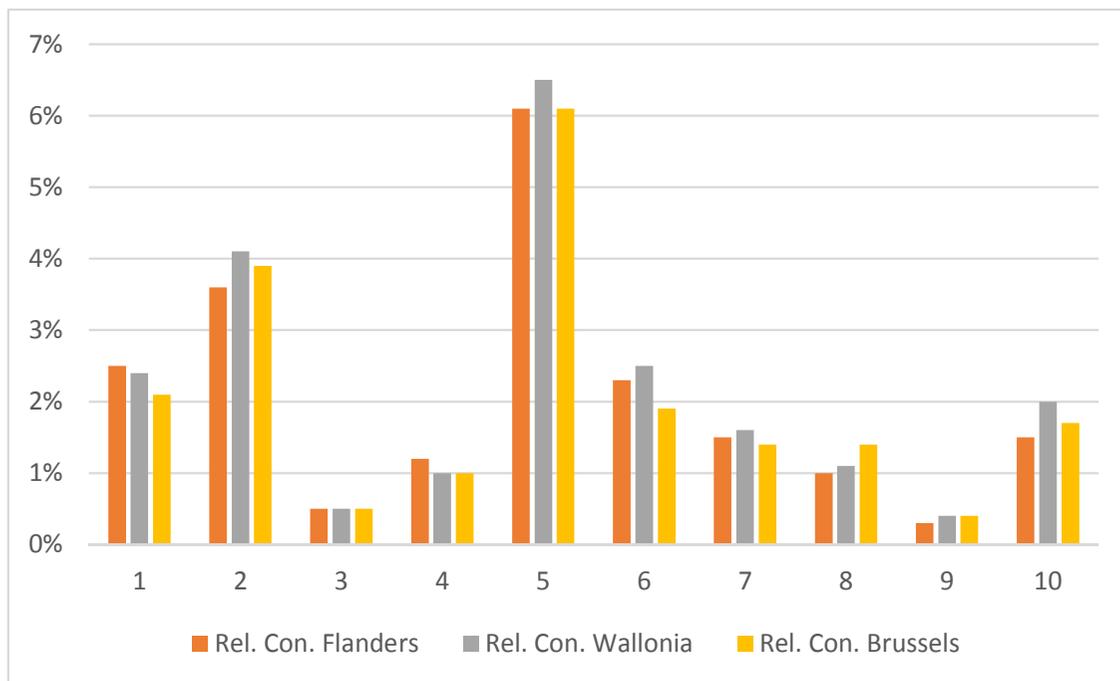
Figure 5 – CS rates in the three Belgian regions following the Robson classification



Data source: SPE report (2014)<sup>8</sup> and CEpiP report (2014)<sup>10</sup>



Figure 6 – Relative contribution of CS by the Robson classification in the Belgian regions



Data source: SPE report (2014)<sup>8</sup> and CEpiP report (2014)<sup>10</sup>

Overall, recent CS rates are comparable in the three Belgian regions.

In 2014 they varied from 20.4% in the Brussels Region to 22.2% in Wallonia, with Flanders with 20.6% in between. Remarkable is the large difference across healthcare facilities in all regions ranging from 11.8% to 32.9%.

The real reason is not clear, but this may represent different case mixes or different practices in each healthcare facility.

Across the three regions also the CS rate and the relative contribution using the Robson classification is comparable. In all three regions, a previous caesarean section is the major indication for a next CS. Second in the order is the group of breech presentations (composed of categories 6 and 7).

Also remarkable is the relation between elective and emergency CS. While in Flanders the majority of CS is elective, the proportion of elective and emergency CS in Wallonia and the Brussels region is almost equal.



## 4 LITERATURE REVIEW ON CAESAREAN SECTION OUTCOMES: METHODS

### 4.1 Introduction

This report was developed using a standard methodology based on a systematic review of the literature. Further details about the KCE methods are available at <https://kce.fgov.be/content/kce-processes>.

### 4.2 Research questions and PICOs

The aim of this report is to provide the evidence for short term and long term outcomes in mothers and their offspring. The clinical research question was formulated using the PICO (Participants–Interventions–Comparator–Outcomes) framework (Table 1).

Table 1 – Clinical research question

PICO item	Description
<b>Patients</b>	<p>Nulliparous or multiparous low-risk pregnant women at term (<math>\geq 37</math> weeks gestation)</p> <p><i>Definition</i></p> <p>Low-risk births were singleton, term (37-41 weeks' gestation), vertex births, with no reported medical risk factors or placenta praevia and with no prior caesarean section</p> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"><li>• Mothers with underlying diseases including infectious diseases (e.g. HIV, Hepatitis B, bleeding disorders)</li><li>• Mothers at moderate or high risk</li><li>• Multiple gestation</li><li>• Women with pre-term birth</li><li>• Fetal conditions such as distress, (very) low birth weight, abnormal or indeterminate fetal heart rate tracing and suspected fetal macrosomia</li><li>• Breech presentation only</li></ul>



PICO item	Description
<b>Interventions</b>	<p>Caesarean section</p> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"> <li>• Repeat caesarean sections (after a previous caesarean delivery)</li> <li>• Interventions to reduce maternal morbidity after CS (techniques for assisting difficult delivery, mechanical dilatation of the cervix at non-labour CS, skin preparation for preventing infection, antibiotic prophylaxis, techniques for repair of the uterine incision and skin closure, type of anaesthesia)</li> <li>• Interventions to reduce children morbidity after CS (corticosteroids for preventing neonatal respiratory morbidity)</li> <li>• Techniques used to perform the caesarean section (e.g. transverse incisions, abdominal incisions)</li> </ul>
<b>Comparators</b>	<p>Vaginal delivery (spontaneous, induced or assisted)</p> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"> <li>• None</li> </ul>
<b>Outcomes</b>	<p>All short term and long term clinical outcomes (physical or psychological) related to the mother or the offspring</p> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"> <li>• No clinical diagnosis (only biological measures such as fractional exhaled nitric oxide (FeNO) instead of asthma)</li> </ul>
<b>Design</b>	<p>RCTs, observational studies (prospective or retrospective cohort studies, case-control studies) conducted in high-income countries</p> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"> <li>• Studies conducted in low-income countries where the mortality related to the pregnancy is very high (e.g. specific African or Asian countries)</li> <li>• Letters to editors, case series, congress abstracts</li> </ul>



## 4.3 Literature search strategy

### 4.3.1 Iterative approach

A search for recently published (from 2011 onwards) systematic reviews and meta-analyses (SR/MA) was performed on 2 February 2016. The selected evidence synthesis was updated by a search for relevant primary studies (RCTs and observational studies) citing the selected SR/MA in Scopus. The latest consultation of Scopus was performed during May 2016.

If no systematic review was available for a specific outcome, a search for publications (systematic reviews and primary studies) was performed on a larger period (15 years). The reference lists of included studies were checked for relevant publications that may have been missed through the database search. Experts in the field were also consulted to identify additional relevant publications that may have been missed.

### 4.3.2 Databases and limits

The following databases were searched for systematic reviews:

- The Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database)
- Medline (including In-process, non-indexed citations and daily updates segments)
- Embase

The following databases were searched for primary studies:

- CENTRAL
- Medline (including In-process, non-indexed citations and daily updates segments)

A combination of appropriate MeSH terms and free text words was used. The search strategies can be found in the supplement (Appendix 2).

### 4.3.3 Studies selection

Studies selection was performed by one researcher in two phases. Phase one consisted of screening the titles and abstracts of the retrieved studies and excluding studies for which it was obvious that they did not fulfill the inclusion criteria. Of the remaining studies (phase two), the full text was screened. If no full-text was available, the study was dismissed. Studies published in a language other than English, Dutch or French were not included for pragmatic reasons.

### 4.3.4 Quality appraisal

Retrieved publications were distributed among three researchers. Each study was appraised for methodological quality by one researcher. Questions and doubts about the evaluation of some criteria were discussed with the other researchers.

The quality of systematic reviews was assessed by using the AMSTAR tool ([http://amstar.ca/Amstar\\_Checklist.php](http://amstar.ca/Amstar_Checklist.php)).<sup>11, 12</sup>

For RCTs the Cochrane Collaboration's tool for assessing risk of bias was to be used, however, no valid RCTs were identified.<sup>13, 14</sup> Also for the assessment of the quality of comparative observational studies the Cochrane Collaboration's tool for assessing risk of bias was used.

Quality appraisal overviews can be found in the supplement (Appendix 3).



#### 4.4 Data extraction

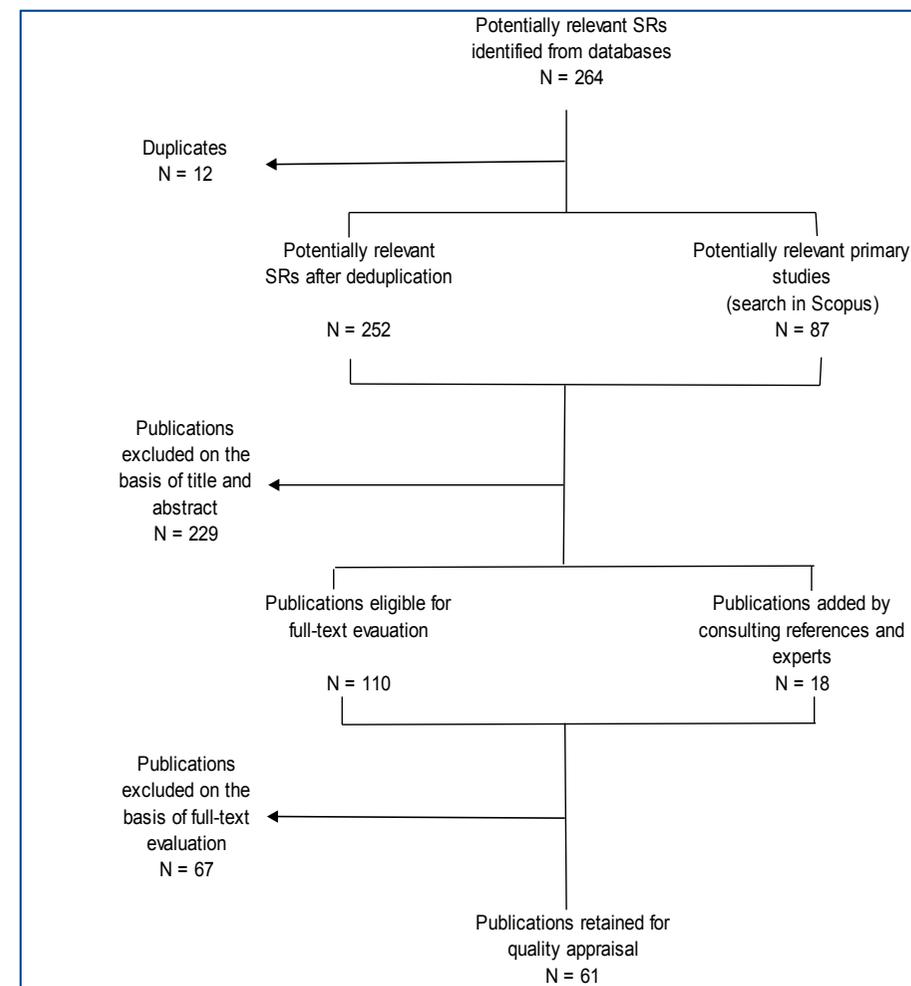
Data extraction was performed by three researchers and entered in the evidence tables using standard KCE-templates. Any questions were answered by discussion after independent reviewing. Evidence tables can be found in the supplement (Appendix 4).

For systematic reviews and meta-analyses the following data are extracted: title and reference, funding sources, search date, databases being searched, number and types of included studies, details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics, details of the intervention and comparator groups that have been addressed in the review, results for the outcomes as defined in the various RQs, and limitations and other comments regarding the review.

For each primary study the following data are extracted in the reference tables: title, reference, type of study, source of funding, country and setting, sample size, duration and follow-up, details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics, details of the intervention and comparator (e.g. standard vaginal delivery, instrumental vaginal delivery (IVD: assisted forceps or vacuum delivery), emergency CS i.e. unplanned CS due to complications (for example fetal distress), elective CS i.e. planned CS with or without medical indication and maternally requested CS). Additionally, results and limitations and other comments regarding the study are recorded in those evidence tables. For observational studies the results adjusted for confounders are reported if presented in the original study. Important confounders to be considered depend on the research question, but include (amongst others) maternal age, maternal BMI, maternal smoking behaviour, pre-pregnancy maternal diseases, previous delivery by caesarean section, marital status, parity and others. In general, paternal potential confounders are not taken into account in those studies.

#### 4.5 Search results

Figure 7 – Flow chart of literature search





## 5 SHORT-TERM MATERNAL OUTCOMES

### 5.1 Maternal morbidity

#### 5.1.1 Background

The causes of maternal morbidity are numerous and complex and cover a wide range of diagnoses. Their duration and severity are highly variable. Maternal morbidity can be conceptualized as a spectrum ranging from non-life-threatening minor morbidity to the near death of a woman who has survived a complication occurring during pregnancy or childbirth or within 42 days of the termination of pregnancy.<sup>15</sup> Fluctuating definitions of non-severe or non-life threatening maternal morbidity continue to exist, sometimes including discomfort (such as nausea) as morbidity.<sup>15</sup>

The Maternal Morbidity Working Group (WHO) has agreed on the following definition of maternal morbidity as: "...any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing...".<sup>15</sup>

Maternal complications include haemorrhage requiring hysterectomy, haemorrhage requiring blood transfusion, hysterectomy, uterine rupture, anaesthetic complications, obstetric shock, cardiac arrest, acute renal failure, assisted ventilation or intubation, puerperal venous thromboembolism, major puerperal infection, in-hospital wound disruption and haematoma.<sup>16</sup>

#### 5.1.2 Systematic review

In 2004, NICE published a clinical guideline on CS which was updated in 2011.<sup>17</sup> One of the main research questions was: 'What are the risks and benefits of planned CS compared with planned VD for both women and children?' Published evidence was identified by applying systematic search strategies through the major databases: Medline, Medline In-Process, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects). The searches were conducted for the original version in 2004, updated and re-executed to include evidence

published and indexed in the literature databases until 17 March 2011. For maternal outcomes, evidence for low risk women was identified from five studies, comparing outcomes for planned CS with planned VD, that is, the comparison is based upon what was planned antenatally, not the actual mode of birth. This mirrors the risks and benefits as they appear to a woman planning birth and take into account that when planning a VD, the woman may give birth by emergency CS (usually carried out during labour).

Results are reported for outcomes for which no more recent systematic review was identified. The quality of the evidence was low or very low for all studies included (see supplement – Appendix 3).

Post-partum haemorrhage and blood transfusion were analysed in a 2014 systematic review and meta-analysis (see description under 5.2.2).<sup>18</sup>

#### 5.1.2.1 Perineal and abdominal pain during birth

One study by Schindl et al. (2003) found that the median pain level during birth (Visual Analog Scale (VAS); median score = 1.0 vs 7.3; range of scores: 0-10; lower values indicate lower pain) and 3 days postpartum (median score = 4.5 vs 5.2) was lower in women who had a planned CS compared with those who had a planned vaginal birth.<sup>19</sup> This finding was statistically significant ( $p \leq 0.05$ ). The same study did not find a statistical difference between the two groups at 4 months postpartum (median score = 0.0 vs 0.17;  $p=0.19$ ). The median scores were calculated by the NICE team.

#### 5.1.2.2 Post-partum haemorrhage and blood transfusion

From observational studies, combined RR revealed no difference in risk of post-partum haemorrhage (RR 1.15; 95% CI [0.40, 3.31]) and blood transfusion (RR 0.91; 95% CI [0.39, 2.13]) between the two groups. Nevertheless, the authors concluded that existing evidence syntheses are misleading as they were based on relatively low-quality studies and misrepresent antenatal planned mode of delivery; therefore, the current available evidence is limited in clinical applicability to steer clinical practice.



### 5.1.2.3 Injury to bladder/ureter

One study by Dahlgren et al. (2009) did not find a statistically significant difference in the incidence of injury to the bladder/ureter for women with a planned CS (0%) compared with women with a spontaneous vaginal birth (0.15%).<sup>20</sup>

### 5.1.2.4 Injury to cervix

One study by Dahlgren et al. (2009) did not find a statistically significant difference in the incidence of injury to the cervix for women with a planned CS (0%) compared with women with a spontaneous vaginal birth (0.24%).<sup>20</sup>

### 5.1.2.5 Injury to vagina

One study by Dahlgren et al. (2009) did not find a statistically significant difference in the incidence of injury to the vagina for women with a planned CS (0%) compared with women who had a spontaneous vaginal birth (0.50%).<sup>20</sup>

### 5.1.2.6 Iatrogenic surgical injury

One study by Dahlgren et al. (2009) did not find a statistically significant difference in the rate of iatrogenic surgical injury for women with a planned CS (0%) compared with women with a spontaneous vaginal birth (0%).<sup>20</sup>

### 5.1.2.7 Deep vein thrombosis

One study of very low quality by Liu et al. (2007) found that the rate of deep vein thrombosis (DVT) was higher in women who had a planned CS (0.06%) than in women with a planned vaginal birth (0.03%).<sup>16</sup> This finding was statistically significant (OR 2.2; 95% CI [1.5, 3.2]; absolute risk difference 0.03 [0.01, 0.06]). Another study from Dahlgren et al. (2009) did not find a statistically significant difference in rates of DVT between women who had a planned CS (0%) and those who had a spontaneous VD (0%).<sup>20</sup>

### 5.1.2.8 Pulmonary embolism

One study by Dahlgren et al. (2009) did not find a statistically significant difference in the rate of pulmonary embolism for women with a planned CS (0%) compared with women with a spontaneous vaginal birth (0%).<sup>20</sup>

### 5.1.2.9 Wound and postpartum infection

One study of very low quality by Liu et al. (2007) found that the rate of wound and postpartum infection was higher in women who had CS without labour (0.6%) compared with women who had a planned vaginal birth (0.21%).<sup>16</sup> This finding was statistically significant (OR 3.0; 95% CI [2.7, 3.4]; absolute risk difference 0.43 [0.36 to 0.51]).

One other study by Dahlgren et al. (2009) found a statistically significant difference in the rate of wound infection between women who had a planned CS and those who had a planned vaginal birth (0.96% vs. 0.18%; RR 5.23; 95% CI [2.13, 12.86]) but not in the rate of postpartum infection (0.1% vs. 0.12%; RR 0.79; 95% CI [0.06, 10.89]).<sup>20</sup>

Two studies by Geller et al. (2010) and Allen et al. (2006) did not find a statistically significant difference in the rate of wound infection for women with a planned CS compared with women with a planned vaginal birth.<sup>21, 22</sup>

### 5.1.2.10 Anaesthetic complications

One study of very low quality by Liu et al. (2007) found that the number of women experiencing anaesthetic complications was higher among women who had CS without labour (0.53%) than among women who had a planned vaginal birth (0.21%).<sup>16</sup> This finding was statistically significant (OR 2.3; 95% CI [2.0, 2.6]; absolute risk difference 0.27 [0.22 to 0.34]). One other study by Dahlgren et al. (2009) found no statistically significant difference (RR 2.79; 95% CI [0.72, 10.89]) in anaesthetic complications between women who had a planned CS (0.38%) and those who had a planned vaginal birth (0.14%).<sup>20</sup>

### 5.1.2.11 Intraoperative trauma

One study by Allen et al. (2006) did not find a statistically significant difference in the rate of intraoperative trauma for women with a planned CS (0.1%) compared with women with a planned VD (0.3%).<sup>22</sup>

### 5.1.2.12 Assisted ventilation or intubation

One study of very low quality by Liu et al. (2007) found that more women who had a CS without labour (0.01%) required assisted ventilation or intubation compared with women who had a planned VD (0.005%).<sup>16</sup> This finding was not statistically significant (OR 2.0; 95% CI [0.9, 4.5]).



### 5.1.2.13 Acute renal failure

One study of very low quality by Liu et al. (2007) did not find a statistically significant difference in the rate of acute renal failure for women with a planned CS (0.004%) compared with women with a planned vaginal birth (0.001%).<sup>16</sup>

### 5.1.2.14 Cardiac arrest

One study of very low quality by Liu et al. (2007) found that more women who had a CS without labour (0.19%) experienced cardiac arrest compared with women who had a planned vaginal birth (0.03%).<sup>16</sup> This finding was statistically significant (OR 5.1; 95% CI [4.1, 6.3]; absolute risk difference 0.16 [0.12 to 0.21]).

### 5.1.2.15 Obstetric shock

One study of very low quality by Liu et al. (2007) did not find a statistically significant difference in the rate of obstetric shock for women with a planned CS (0.01%) compared with women who had a planned VD (0.02%).<sup>16</sup>

### 5.1.2.16 Peripartum hysterectomy

One study of very low quality by Liu et al. (2007) measured two outcomes: haemorrhage requiring hysterectomy and any hysterectomy.

In this study more women who had a CS without labour (0.03%) experienced haemorrhage requiring hysterectomy compared with women who had a planned vaginal birth (0.01%).<sup>16</sup> This finding was statistically significant (OR 2.1; 95% CI [1.2, 3.8]; absolute risk difference 0.01 [0.002 to 0.03]). In the same way, more women who had a CS without labour (0.06%) experienced any hysterectomy compared with women who had a planned vaginal birth (0.02%).<sup>16</sup> This finding was statistically significant (OR 3.2; 95% CI [2.2, 4.8]; absolute risk difference 0.04 [0.02 to 0.06]).

Authors highlighted a paradox: planned CS was associated with an increased risk of haemorrhage requiring hysterectomy, whereas haemorrhage requiring blood transfusion was more commonly associated with a planned VD. Although this paradox might reflect inherent uterine pathology, such pathology is rare.

Observational studies that evaluated the impact of the mode of delivery on maternal morbidity are scarce. Only five studies reported maternal morbidity outcomes for women with an uncomplicated pregnancy and no previous CS. For each outcome of interest, NICE reported a low to very low level of evidence, using the GRADE methodology.

Studies suggested that the **following outcomes may be reduced after a planned CS**: perineal and abdominal pain during the birth and persisting 3 days post-partum.

Studies suggested that the **following outcomes may be increased after a planned CS**: cardiac arrest, peripartum hysterectomy.

**No differences** were found between planned CS and planned vaginal birth for the following outcomes: perineal and abdominal pain 4 months post-partum, injury to bladder/ureter, injury to cervix, injury to vagina, iatrogenic surgical injury, pulmonary embolism, intraoperative trauma, assisted ventilation or intubation, acute renal failure and obstetric shock.

**Inconsistent findings** were reported among studies for the following outcomes: deep vein thrombosis, infection wound and post-partum and anaesthetic complications.

## 5.2 Maternal mortality

### 5.2.1 Background

The frequency of elective primary caesarean section delivery (CS) has risen in recent decades, owing in part to the common opinion that this surgical procedure is of little or no risk to healthy women. While in the past, a CS was restricted to specific cases (obstetrical complications or medical illness), elective primary CS deliveries with no clear medical or obstetric indication are increasingly performed.<sup>16</sup> Clinicians and researchers, worried about this increase attempt to assess the risks of maternal complications and death associated with elective CS performed in healthy women with normal pregnancies.



### 5.2.2 Systematic review

One systematic review was identified and retrieved.<sup>18</sup> This systematic review (SR) aims to determine whether maternal outcomes are better with antenatal decision to give birth by CS compared to vaginal delivery (VD), in singleton pregnancies in low-risk women. The main outcome measures were **maternal mortality and severe morbidity**. This SR includes seven primary studies (of which two assess the maternal mortality), and one multicentre international randomized controlled trial (RCT) (The Term Breech Trial; n=2083 women) where women were randomized to planned CS or planned VD.

Observational evidence comes from two observational studies:

- In Liu et al. (2007, Canadian Registry data; 46 766 women in elective CS group v. 2 292 420 in elective VD group): No mothers died in-hospital in the planned caesarean delivery group, whereas 41 women died in the planned vaginal delivery group (mortality rate 1.8 per 100 000 deliveries; p = 0.87).
- In Kor-Anatakul et al. (2008, 1 hospital-based study in Thailand; 1429 cases, 1242 elective VD and 187 elective CS): Two maternal deaths occurred in the VD group that had required an unscheduled caesarean delivery. The causes of the deaths were amniotic fluid embolism and intracerebral haemorrhage.

A maternal death has become gradually rare in most European and other industrialized countries. The main causes of pregnancy related deaths include cardiovascular disease, infection or sepsis, and haemorrhage. Medical experts consider that a number of issues, including obesity-related complications such as hypertension and diabetes, the sharp increase in the number of caesarean section births, a lack of access to affordable, quality health care and more women giving birth at older ages could gradually increase the maternal death rates in these countries.

For the relation between mode of delivery (caesarean section vs. vaginal delivery) and maternal mortality, both experimental (for breech presentations) and observational evidence were analysed in one systematic review. No significant difference in risk of maternal mortality between the two groups was reported.

**Main conclusion: existing evidence syntheses are misleading as they were based on relatively low-quality studies and misrepresent antenatal planned mode of delivery; therefore, the current available evidence is limited in clinical applicability to steer clinical practice.**

## 5.3 Breastfeeding

### 5.3.1 Background

From 1990 until 2011, several studies attempted to assess the impact of CS on breastfeeding but results were inconsistent (some studies reported no association and others an inverse relation). The reason is that some modes of delivery, such as CS, is usually assumed to adversely impact breastfeeding. Two biological mechanisms can explain this association. The first is associated with surgery. After an emergency CS, some complications can occur such as pain, haemorrhage, and infections, susceptible to delay mothers holding their infants and disrupt mother-infant interaction. Moreover, in-labour CS may be performed after a long, difficult labour and be followed by numerous factors such as confinement to bed, fasting, analgesia and/or anaesthetics for pain, and additional anxiety and stress, all having an adverse impact on breastfeeding. For elective CS, performed before the onset of labour, such complications are limited but postoperative care routines after CS also interrupt bonding. Because the first postnatal hours are crucial for establishing mother-infant interaction and guarantee breastfeeding success, vaginally delivered infants have more chances to start early and effective breastfeeding. The other biological mechanism is related to the magnitude of oxytocin and prolactin responses, playing important mediating roles in milk ejection and in establishing mother-infant interaction, would differ between modes of delivery. Blood concentrations of



appetite-regulating hormones in infants born by CS and VD would also be different and could hamper a successful breastfeeding.<sup>23</sup>

Given the generally accepted health benefits of breastfeeding, understanding the impact of mode of delivery is relevant to pregnant women and health care providers worldwide.

### 5.3.2 Systematic reviews and meta-analyses

One moderate quality systematic review (Amstar 7/11) was identified and retrieved.<sup>24</sup> The aim of this SR and MA from Prior et al. (2012) was to determine the association between mode of delivery and early breastfeeding as well as continuation of breastfeeding until 6 months postpartum.

This SR included 48 studies (retrospective or prospective cohort studies conducted in 31 countries throughout the world, n= 553 306 subjects) in which some or all data were suitable for inclusion in the meta-analysis. No quality appraisal of the included studies was performed and the heterogeneity between studies was very high. Therefore, random-effects analysis was performed. Most of studies included primiparous and multiparous women, full-term birth or not. No sensitivity analyses were conducted for elective CS in these subgroups. Funnel plots for early breastfeeding showed strong visual evidence of publication bias, confirmed by Egger's test ( $p = 0.007$ ). This may have led to an overestimation of the effect size.

After adjustment for factors associated with early breastfeeding, the rate of early breastfeeding was lower after CS (pooled OR: 0.61; 95% CI [0.50, 0.75]), whether the CS was elective or conducted in emergency. Elective CS was associated with a significant reduction in early breastfeeding when compared with VD (8 studies; pooled OR: 0.83; 95% CI [0.80, 0.86]). Nevertheless, when breastfeeding is initiated, mode of delivery has no apparent effect on the number of mothers still breastfeeding at 6 months.<sup>24</sup>

### 5.3.3 Update with primary studies

From 59 papers identified, 2 cohort studies were retained after having conducted their quality appraisal.<sup>25, 26</sup>

In the study by Watt et al. (2012), 2560 women were included, aged 16 years or older who delivered live, full-term ( $\geq 37$  completed weeks), singleton infants, from 11 hospital sites in Ontario, Canada.<sup>26</sup> Data collection began in April 2006 and ended in October 2008. Both exposure (mode of delivery) and outcomes (infant feeding) were captured by a self-reported Mothers' Questionnaire (n = 2560 women) and a follow-up structured telephone interview 6 weeks after hospital discharge (n= 1897; 74.1%). From these, 33.1% had a CS, 51.7% of which were planned before labour began. Breastfeeding initiation was reported by 92.3% of interviewees. Breastfeeding continuation declined to 74.3% by 6 weeks postpartum. This study found no association between breastfeeding initiation at hospital and planned CS compared to vaginal unassisted delivery (OR = 0.9731, 95% CI [0.7651, 1.2377]). Similarly, breastfeeding at 6 weeks was not associated with the method of delivery (CS vs. VD), nor was it associated with vaginal or caesarean delivery subtypes (assisted/non-assisted VD or planned/unplanned CS) for caesareans (OR = 0.9190, 95% CI [0.7592, 1.1124]).

Women who had an unexpected delivery method were more likely to have pursued breastfeeding to 6 weeks than were women who had experienced their anticipated delivery method. An unexpected delivery method (unplanned CS or IVD) is more stressful for women who saw it as a risk to them but also to their infant. Breastfeeding initiation could be seen as a coping strategy allowing the new mothers to resume control on their own life and normalize an abnormal experience.

In this study, the authors concluded that it is not the method of delivery in itself that influences breastfeeding initiation and continuation but rather the change in anticipated delivery method.



Regan et al. (2013), conducted a population-based retrospective cohort study (2006-2007) with low risk of bias focused on breastfeeding in women with a prior CS (n= 280 882) live-born singletons.<sup>25</sup> Of those, 201 560 (71.8%) were VD, 50 912 (18.1%) were primary CS, and 28 090 (10.0%) were repeat CS. The study concluded that women who attempted and succeeded in achieving VD after a previous CS were more likely to initiate breastfeeding than women who underwent a scheduled repeat CS (adjusted relative risk 1.47; 95% CI [1.35, 1.60]). Women who ultimately delivered by CS with unsuccessful trial of labour were also more likely to breastfeed than women with a scheduled repeat CS (adjusted relative risk 1.17; 95% CI [1.04, 1.33]). Other potential factors are found to be negatively associated with the breastfeeding initiation: certain demographic characteristics including younger maternal age, increased BMI, lower parity, tobacco use, and number of prior CS. Moreover, patients with low socio-economic status, who did not receive prenatal care (support through education and provider encouragement), and with chronic hypertension were also less likely to initiate breastfeeding.

For the relation between breastfeeding and (elective) caesarean section vs. vaginal delivery, only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

Studies that evaluated the impact of the mode of delivery on breastfeeding initiation and continuation produced inconsistent results. In some studies, negative associations were found between elective caesarean delivery and breastfeeding initiation whereas in other studies, such association is not confirmed. Once initiated, breastfeeding at 6 months does not appear to be affected anymore.

It is important to point out that methodologies used by all primary studies included (both in the systematic review and in the update) were really diverse and mostly based on questionnaire-based interviews. Lots of countries, either developed or developing countries, were involved and no study investigated the association between mode of delivery and breastfeeding in 'Baby friendly hospitals' where a high level of breastfeeding support is provided by the health personnel (UNICEF and WHO initiative; see <http://www.unicef.org/programme/breastfeeding/baby.htm>).

It is argued that in such hospitals, the encouragement and support received from healthcare providers can motivate all mothers to initiate and maintain breastfeeding, regardless of delivery mode.



## 6 LONG-TERM MATERNAL OUTCOMES

### 6.1 Urinary incontinence

#### 6.1.1 Background

Pregnancy is a recognised risk factor for urinary incontinence both among young and middle-aged women.<sup>27-29</sup> Childbearing itself may cause hormonal fluctuations, mechanical changes, or both that can cause urinary incontinence. Mode of delivery can also be related to postpartum urinary incontinence, vaginal delivery being suspected to be the main contributing factor, probably because of damage to the pelvic floor, weakening bladder neck support<sup>30</sup> and compromising innervation.<sup>31</sup> Caesarean delivery, particularly prelabour caesarean, is assumed to offer substantial protection against such pelvic floor trauma; in contrast, assisted vaginal delivery, with vacuum or forceps, is believed to carry increased risks of trauma.<sup>32</sup>

#### 6.1.2 Systematic reviews and meta-analyses

One high quality systematic review by Tähtinen et al. (Amstar 10/11) with meta-analysis was identified and retrieved.<sup>32</sup> This systematic review examined the association between delivery mode and the presence of Stress urinary incontinence (SUI) and Urgency urinary incontinence (UUI) >1 year after delivery. SUI is defined as the involuntary loss of urine on effort or physical exertion, or on sneezing or coughing while UUI is defined as involuntary loss of urine associated with a sudden and compelling desire to pass urine.

Only results originating from studies that compared elective caesarean delivery and vaginal delivery are reported here (in total, this SR identified 11 different comparisons between delivery modes assessing risk of SUI and 5 different comparisons assessing risk of UUI).

When comparing elective caesarean with the decision made before the onset of labour only, two (both high risk of bias) studies reported a risk of SUI over three times higher **with vaginal delivery** (aOR: 3.53; 95% CI [2.55, 4.90]; heterogeneity:  $p = 0.84$ ;  $I^2 = 0\%$ ; risk difference: 10.7%). No study reported the impact of elective caesarean only versus vaginal delivery on UUI. The risk of UUI was modestly increased after vaginal delivery when

compared with all kinds caesarean delivery (aOR: 1.30; 95% CI [1.02, 1.65]; heterogeneity:  $p = 0.14$ ;  $I^2 = 37\%$ ; risk difference: 2.6%).

Authors of this systematic review recognize following limits and methodological weaknesses: mean age and parity of study populations, case definition of SUI and UUI, definition of vaginal delivery groups, risk of bias, and survey methods varied across studies; most primary studies combined all caesarean sections, irrespective of timing; the effect estimates in the analysis comparing elective caesarean and vaginal delivery were imprecise due to a lack of statistical power.

Incontinence is common among women irrespective of delivery history. The prevalence estimates vary widely according to the study designs and definitions used to capture urinary incontinence (UI). A recent French epidemiological study compared data from five national surveys using different designs and UI definitions and reported an UI prevalence around 17% in the representative samples.<sup>33</sup>

A very recent systematic review examined the association between delivery mode and the presence of urinary incontinence >1 year after delivery. Meta-analysis of data from two (both high risk of bias) studies demonstrated a threefold increase in the risk of developing long-term stress urinary incontinence (SUI), an absolute increase >10% in moderate or severe SUI, when comparing non-instrumental vaginal delivery with elective caesarean section. The effect is largest in younger women but diminishes with age. The odds of urgency urinary incontinence (UUI) is also increased after vaginal delivery, but no study reported the specific impact of *elective* caesarean delivery versus vaginal delivery on UUI. The delivery mode would have only a small impact on UUI at a population level.

**Main conclusion: there is observational evidence of an association between urinary incontinence and non-instrumental vaginal delivery. However, the causal nature of this association is difficult to prove.**



## 6.2 Faecal incontinence

### 6.2.1 Background

Faecal incontinence is defined as the complaint of involuntary loss of faeces while anal incontinence is the complaint of involuntary loss of faeces or flatus. It is considered as a consequence of labour and vaginal delivery<sup>34</sup> and may occur in women during the immediate postpartum period or persisting throughout life. Some obstetricians argue that vaginal delivery affects both urinary and anal continence, with some advocating CS to protect the pelvic floor and anal continence mechanism.<sup>35</sup>

### 6.2.2 Systematic reviews

One high quality Cochrane systematic review by Nelson et al. (Amstar 9/11) was identified and retrieved.<sup>36</sup> This systematic review aims to include both randomised and non-randomised studies that allowed comparisons of postpartum anal continence (both faecal and flatus) in women who had had babies delivered by either (elective or emergency) CS or VD. This review includes 21 published studies, involving 31 698 women, delivered through 6 028 CS and 25 170 VD. While a large number of deliveries were included in this review, many of the studies were small and may not have had sufficient statistical power to demonstrate a benefit. Only one report randomised women (The Breech Trial) to CS or VD.

For assessment of anal incontinence, a variety of methods were used and included maternal self-reporting to mailed questionnaires. Only five studies used an instrument specifically validated for anal continence assessment. Two studies failed to separate anal incontinence, i.e. presented a combined flatus/faecal outcome. Moreover, a lot of studies made their unique assessment within four months of the baby being born: too soon for vaginal/rectal healing.

Reported crude incontinence rates varied significantly between studies, from 14% to 48%. Such variation is disturbing and can be explained by a large clinical heterogeneity due to the outcomes evaluation methods and the age of the assessed populations. However, statistical heterogeneity was not

assessed in this review since the studies were all considered to be non-randomised.

Because all studies were non-randomised, no meta-analysis was performed to calculate a summary relative risk among studies. The review incorporated bias measures, such as adjustments for age and parity, pregnancy and delivery history, a separate analysis of emergency and elective CS, and the timing of assessment of pelvic function and continence. Forest plots using Revman Analysis without summary statistics are reported in the Cochrane review. Two of them were copy-pasted here:

1. Faecal incontinence in the 7 best studies, i.e. those studies which fulfilled the three following criteria: age adjustment, assessment of incontinence after 4 months postpartum and women categorized as CS with no history of prior VD (Figure 8);
2. A comparison of elective CS versus non-instrumental VD for the outcome of faecal incontinence (Figure 9).

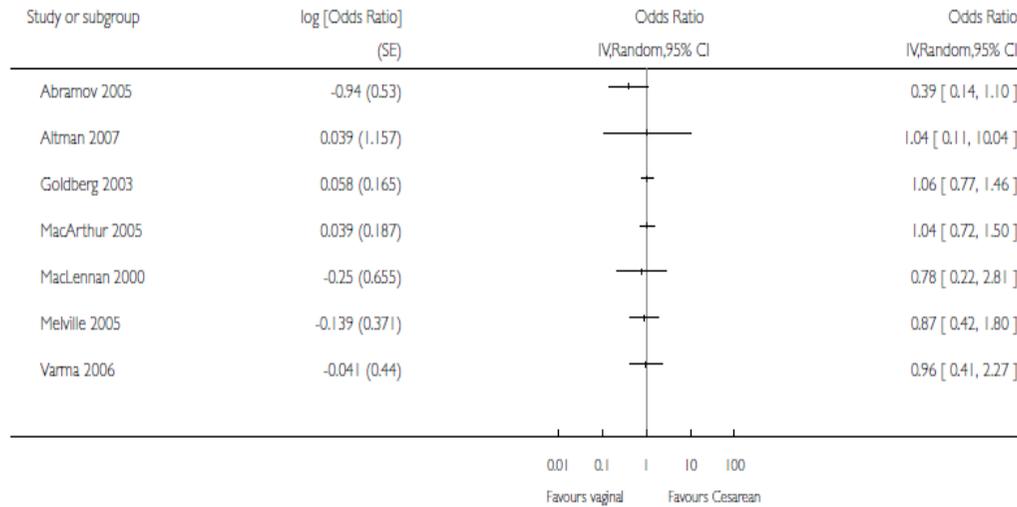
Seven studies adjusted for age, avoided misclassification or overlap of delivery mode, and assessed incontinence at an appropriate time. A validated instrument for the detection of anal incontinence was used in four of these studies (Abramov 2005; Altman 2007; Goldberg 2003; Melville 2005). None of these studies showed a significant benefit of CS over VD and aside from Abramov (2005), the odds ratios are closely clustered around 1.0, although none of them were statistically significant.

Four studies presented analyses that compare elective CS versus VD. There was no significant advantage of elective CS over VD in any of these four studies.

An older systematic review from Pretlove et al. (2008) was identified, that included 18 observational studies.<sup>35</sup> Women having any type of IVD (forceps and/or suction delivery) were compared with a CS or a spontaneous vaginal delivery (SVD). Only two studies compared SVD with CS. The systematic review of Nelson being the more recent and comprehensive one, we decided not to report results from the Pretlove systematic review.

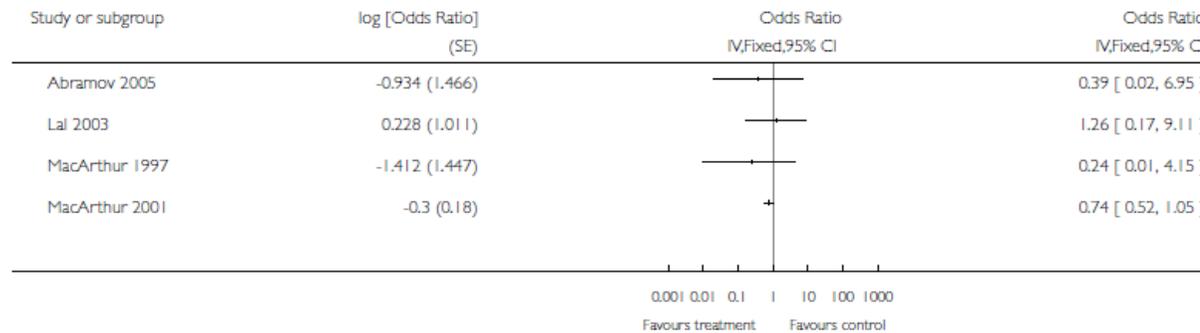


**Figure 8 – Subgroup Analysis: VD vs. CS, Outcome Incontinence of Faeces; 7 best studies.**



Source: Nelson et al. (2010)<sup>36</sup>

**Figure 9 – Subgroup Analysis: VD vs. CS, Outcome 3 Elective CS versus VD**



Source: Nelson et al. (2010)<sup>36</sup>



### 6.2.3 Update with primary studies

One subsequent twelve-year longitudinal study was published by MacArthur et al. (2011).<sup>37</sup> This study investigated the association between delivery mode history and urinary (UI) and faecal incontinence (FI), specifically in women with a history of exclusive CS deliveries. The study was conducted in maternity units in Aberdeen (UK), Birmingham (UK) and Dunedin (New Zealand). All mothers giving birth at one of those three maternity units (n=10 989) were sent a postal questionnaire at 3 months postpartum. Of these 7 879 replied (72% response rate). Follow-up questionnaires were sent at 6 and 12 years post-partum. This study was large and of long duration. At 12 years the prevalence of faecal incontinence was 12.9%. However, at that moment the response rate had dropped to 34% of the original eligible sample. After adjustment for parity, BMI and age at first birth, there was no difference in FI between women who exclusively delivered through CS vs. women with only SVD (aOR 0.94; 95% CI [0.66, 1.33]) or women who delivered through a mixed SVD + CS vs. women only SVD (aOR 1.06; 95% CI [0.73, 1.54]). Only a limited set of confounders was used for the adjustments. Moreover, the outcomes were self-reported by a unique question about occurrence and frequency of faecal incontinence by postal questionnaire.

For the relation between anal incontinence with (elective) caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

The Cochrane review of caesarean delivery for the prevention of anal incontinence found that the likelihood of faecal incontinence (FI) following an index birth by caesarean section was no different than following a vaginal delivery.

No studies showed a significant benefit of caesarean delivery over vaginal delivery in relation to continence or flatus.

Some studies merged faecal incontinence and flatus as a unique outcome measure when using a continence assessment tool; consequently, the results of anal incontinence post-vaginal delivery varied widely to as high as 48%.

Six studies compared emergency versus elective caesarean delivery. These studies separated pregnancy factors from the influence of labour on pelvic floor function. There was no significant difference in faecal incontinence between women having either type of caesarean delivery. No significant difference in faecal incontinence was reported between an elective caesarean delivery and a vaginal delivery.

**Main conclusion: none of the studies show compelling evidence that there is an association between anal incontinence and mode of delivery.**

## 6.3 Postnatal depression

### 6.3.1 Background

A complicated labour or an emergency CS can be very stressful to the mother. In such scenarios there may be an association between emergency operative delivery and postnatal depression. Several studies have investigated this association, though the current evidence is conflicting, with some studies reporting an association and others not. Conversely there may also be an association between elective CS and a reduced risk of postnatal depression because delivery was a less traumatic experience.<sup>38</sup>

### 6.3.2 Systematic reviews and meta-analyses

One systematic review (Amstar 9/11) was identified and retrieved.<sup>18</sup> This systematic review with meta-analysis aims to determine whether maternal outcomes are better with antenatal choice to give birth by CS compared to VD, in singleton pregnancies in low-risk women without a subsequent pregnancy. The secondary outcome measures included postnatal depression. This SR included 7 primary studies, of which 6 were observational studies and 1 was a multicentre international randomized controlled trial (The Term Breech Trial; n= 2083 women). Results related to



postnatal depression were only measured in the RCT that included breech presentations only (excluded from our PICO).<sup>39</sup>

### 6.3.3 Update with primary studies

An additional cohort study from Patel et al. (2005) assessed the association between operative delivery and postnatal depression.<sup>38, 40</sup> In this cohort study (n=10 934) there was no evidence that elective CS altered the odds of postnatal depression compared with planned vaginal delivery (aOR 1.06; 95% CI [0.66, 1.70]).

A more recent reference is an Australian study by Hanlon et al. (2015).<sup>41</sup> In this retrospective cohort of term, singleton births during the year 2013 in a single tertiary obstetric facility were included (n=3 021 births). Outcomes were compared for 1 816 women having SVD versus 1 205 women with IVD or CS. After adjusting for all measured confounders, no association between postnatal psychological morbidity in the early postnatal period and mode of delivery is demonstrated. However, this study shows a statistically significant association between nulliparous vs. multiparous women and postnatal depression: aOR 1.69; 95% CI [1.09, 2.63].

For the relation between post-natal depression in relation with caesarean section vs. vaginal delivery, only observational evidence is available.

**Main conclusion: none of the studies show compelling evidence that there is an association between post-natal depression and mode of delivery.**

## 7 IMPACT ON FUTURE PREGNANCIES: MATERNAL OUTCOMES

### 7.1 Subsequent fertility

#### 7.1.1 Background

Compared to standard VD, CS has long been suspected to lead to a reduction in subsequent birth rates and a longer time to next pregnancy. The potential negative association between caesarean delivery and subsequent fertility is of interest because both caesarean section rates and the age of mothers at first birth are continuously rising.<sup>4</sup> Age is not in itself an indication for caesarean section but the occurrence of specific risks (e.g. risk of fetal congenital malformations, hypertension, or diabetes mellitus) in higher age groups (over 35 years old) may represent an indication for CS.<sup>4</sup>

Various mechanisms explaining such delay between two pregnancies after a previous CS may include placental bed disruption and pelvic adhesion as a result of the procedure.<sup>42, 43</sup> Other social and educational factors may play a role in delaying or avoiding a further childbirth including choice to have a small family, women's desire to work (full time or not) or stay longer in education.<sup>44-46</sup>

Because it is somewhat difficult to evaluate the fertility of women after a first birth, rate and time to subsequent live birth were frequently used as surrogate markers of fertility. Several studies have examined the relationship between caesarean section and these surrogates leading to contradictory results.<sup>45-48</sup> Earlier design weaknesses and methodological limitations hampered to draw firm conclusions about this potential association. For example, major key factors allowing to establish whether a Caesarean section impacts the rate and time to subsequent live birth were lacking such as the absence of the indication for mode of delivery, the distinction between elective and emergency caesarean section, the information on a woman's obstetric history including pre-existing subfertility and access to fertility services in the past).<sup>49</sup>



### 7.1.2 Systematic reviews and meta-analyses

Two high quality systematic reviews (Amstar 9/11) with meta-analyses were identified and retrieved.<sup>42, 50</sup>

Gurol-Urgancı included eighteen cohort studies, totalling 591 850 women, from primiparous women with one live singleton to all inclusive.<sup>42</sup> None study excluded women with previous fertility problems. The impact of Caesarean section on subsequent pregnancies could be analysed in 10 studies and on subsequent births in 16 studies. The meta-analysis indicated that women who had undergone a Caesarean section, whether it was planned or not, had a 9% lower subsequent pregnancy rate [risk ratio (RR) 0.91, 95% CI (0.87, 0.95)] and 11% lower birth rate (RR 0.89, 95% CI [0.87, 0.92]) compared with patients who had delivered vaginally. Studies that controlled for maternal age or specifically analysed primary elective Caesarean section for breech delivery (2 studies only) reported smaller effects. There was significant variation in the design and methods of included studies and authors did recognize that research able to limit the impact of selection bias by indication through creating more comparable patient groups and applying risk adjustment are required before drawing any conclusion.

The second systematic review and meta-analysis by O'Neill et al. included 11 studies (10 cohort studies and 1 case-control study).<sup>50</sup> Nine of these studies were also included in the previous SR.<sup>42</sup> Only 5 studies that adjusted for a minimum of three confounders including maternal age confounders were included in the meta-analysis. The indication for mode of delivery (IVD, vaginal breech, elective CS, emergency CS, etc.) was available in only two of the 5 meta-analysed studies and so confounding by indication may also exist in some of the included studies. The meta-analysis reported a 14% reduction in subsequent birth rates following caesarean section, a result similar to the rate reported by the previous SR. However, two major confounders were not investigated: whether women were deliberately delaying pregnancy, and whether any fertility treatment was used by the study populations.

From studies that were not included in the O'Neill meta-analysis:

- One study (547 primiparous women with breech emergency or elective CS) reported a longer inter-pregnancy interval (IPI) following caesarean delivery (elective Caesarean delivery 22 months versus vaginal delivery 16 months). The second study (5513 primiparous women without indication for the CS) reported that a caesarean delivery was not associated with any delay in subsequent IPI. Median IPI in the overall cohort was reported as 21.8 months.
- One study (570 primiparous women without indication for the CS) reported a longer birth interval among women with a Caesarean delivery (5.5% of women with a Caesarean delivery compared to 1.4% of women with a vaginal delivery took more than two years to conceive).
- Two studies (respectively 812 and 12 918 primiparous women without indication for the CS) reported no delay in time to next birth among women with a Caesarean delivery.
- No evidence existed to show that a Caesarean delivery was associated with a longer time to next pregnancy or birth (1 study including 1152 primiparous women for which a CS was undertaken for failure to progress/fetal distress).

### 7.1.3 Update with primary studies

Three additional studies were retrieved and analysed owing their level of quality, published by the same authors who published the systematic reviews.<sup>49, 51, 52</sup>

Gurol-Urgancı (2014) conducted a large retrospective cohort study using a large national data set with detailed information on maternal characteristics and pregnancy outcomes.<sup>51</sup> Following the eligibility criteria (low-risk women admitted in English maternity units for delivery), their cohort totalized 1 047 644 first births covering the period between 1 April 2000 and 31 March 2012. The aim of the study was to evaluate the extent to which the Caesarean section procedure itself was associated with subsequent fertility. Over 60% of the women were <30 years of age when they gave birth. Globally, 782 590 (74.7%) women had a subsequent live birth. The overall Caesarean section rate for the cohort was 21.4%, with <4% of women having an elective Caesarean section (3% in 15-29 years and 7.7% in 35-



40 years). Women with standard vaginal delivery represented 57% of the cohort (62.7% in 15-29 years and 38.9% in 35-40 years). Compared with vaginal delivery, subsequent birth rates were slightly lower after elective Caesarean for breech (adjusted hazard ratio, HR 0.96, 95% CI [0.94, 0.98]). Larger effects were observed after elective Caesarean for other indications (adjusted HR 0.81, 95% CI [0.78, 0.83]), and emergency Caesarean (adjusted HR 0.91, 95% CI [0.90, 0.93]). The effect was smallest for elective Caesarean for breech, and this was not statistically significant in women younger than 30 years of age (adjusted HR 0.98, 95% CI [0.96, 1.01]). Results from a Cox regression model with age category and mode of delivery interaction terms demonstrated that subsequent fertility declines with age, regardless of mode of delivery ( $p < 0.001$  for each pairwise comparison, data not shown). Residual bias in the adjusted results remain possible due to the impossibility to adjust for maternal factors such as obesity and voluntary absence of conception or completely account for history of infertility.

O'Neill et al. (2014) conducted a population registry-based cohort study covering the period from 1982 to 2010 in Denmark ( $N = 832\,996$ ).<sup>49</sup> The aim of this study was to estimate the fecundity (i.e. whether a lower proportion of second live births occurred) in women with a primary Caesarean section compared with spontaneous vaginal delivery (SVD). Globally, 577 830 (69%) women had a subsequent live birth. Women with any type of Caesarean had a lower rate of subsequent live birth (hazard ratio [HR] 0.86, 95% CI [0.85, 0.87]) compared with spontaneous vaginal delivery. This effect was consistent when analyses were stratified by type of Caesarean: emergency (HR 0.87, 95% CI [0.86, 0.88]), elective (HR 0.83, 95% CI [0.82, 0.84]) and maternal-requested (HR 0.61, 95% CI [0.57, 0.66]). Lack of biological data to measure a woman's fertility is a major limitation of the current study. Unmeasured confounding and limited availability of data (maternal BMI, smoking, access to fertility services and maternal-requested Caesarean section) as well as changes in maternity care over time may also influence the findings. The findings of the current study indicate that a prior Caesarean section is associated with a reduction in subsequent births in this Danish population-based cohort.

O'Neill et al. (2015) conducted a large hospital-based cohort study, in Aarhus (Aarhus Birth Cohort (ABC), Denmark).<sup>52</sup> The sample, composed of

over 91 625 women enrolled between September 1989 and December 2010, is therefore a subset of the national data reported in O'Neill (2014), with 21 years of follow-up. This prospective study differs from previous ones in that it includes more detailed information than the national registries; a particular advantage of the ABC cohort is the availability of information on whether the pregnancy was planned, detailed information on mode of delivery and complications of pregnancy, delivery and the postpartum. The lack of knowledge about these factors as well as factors which may influence a woman's decision to have a subsequent child was the main limitation of studies to date. During the whole period, 46 162 index live births were identified, and 22 462 women (49%) had a subsequent live birth during the study period. Different statistical models were reported, adjusting for diverse confounding factors. The model that included the highest number of confounders (maternal age, maternal origin, previous stillbirth, miscarriage or ectopic pregnancy, maternal BMI, fertility treatment in the first birth, smoking (pre- and during pregnancy), birth year, gestational age, birthweight, infant sex, infant length, education and marital status) was tested on 26 949 women included in the study. Women with any type of caesarean (emergency, elective) had a 6% reduction in the rate of subsequent live birth (HR 0.94, 95% CI [0.89, 0.98]) compared with all vaginal deliveries (spontaneous, breech, shoulder dystocia). Analysis by the indication for mode of delivery showed a slightly change for elective CS (HR 0.91, 95% CI [0.85, 0.98]). Further adjusting for a history of macrosomia in the first birth does not change the results (Elective CS: HR 0.92, 95% CI [0.86, 0.99]). However, when the model was adjusted for women who reported planning their first pregnancy, elective caesarean was associated with a 14% reduction in subsequent birth rate (HR 0.86, 95% CI [0.74, 0.99]). Adjustment for prior fertility treatment showed a reduced rate of subsequent live birth, although this was not statistically significant across all modes of delivery. Finally, women with a prior elective caesarean (HR 0.89, 95% CI [0.82, 0.96]) had a significant reduction in the rate of subsequent live birth in a sensitivity analysis excluding women with complications of pregnancy with/without neonatal complications, compared with women with a prior SVD. The median time for a subsequent live birth was 1055 days for elective caesarean (95% CI [1025, 1091]) compared with 1009 days for a spontaneous vaginal delivery (95% CI [1002, 1016]). Authors concluded that



a causal association cannot be ruled out, although the effects of mode of delivery on the rate of subsequent live birth were minimal in this study.

Both meta-analyses reported either a lower subsequent pregnancy rate or a lower birth rate after a Caesarean section, whether it was planned or not, compared with women who had delivered vaginally. Nevertheless significant weaknesses in study designs and analytical methods are reported (e.g. the enrolled population ranged from being all inclusive to being restricted to primiparous women who delivered a live singleton baby at term; only few studies limited the cohort to low-risk pregnancies or reported separately the outcomes for women who had caesarean section for breech presentation). Major confounders were not investigated: whether women were deliberately delaying pregnancy, and whether any fertility treatment was used by the study populations. Underlying mechanisms for an association between caesarean delivery and subsequent sub-fertility remains unclear. Moreover, there was no clear identification of CS for elective and mainly non-medical reason.

Both large retrospective cohort studies provided evidence that there is no or only an insignificant effect of caesarean section on future fertility. Consistent with previous studies, the reported associations may be due to women deliberately postponing or avoiding a following birth, and this may be for a multitude of motives (financial, social, and cultural) as well as the couple's own choice to have a small family. Because subsequent fertility declines with age, regardless of mode of delivery, the older the woman is at the birth of her first baby, the lesser is the probability to have other children.

The prospective cohort study conducted in Denmark is reinforced by data on pregnancy planning as well as information on complications of pregnancy, delivery and neonatal morbidities, all of which may impact a woman's choice for a following birth. The effect of mode of delivery on subsequent rate and time to next birth was minimal. The greatest reduction was among women with assisted vaginal delivery complicated by shoulder dystocia.

The lack of biological data to measure a woman's fertility is a major limitation of all studies under investigation. This is the reason why surrogate markers were used by the authors (inter-pregnancy interval and birth interval), that can be impacted by lots of reasons (medical or not). Even if a longer waiting time to next pregnancy or live birth is stated after a caesarean section, biological, personal or psychological factors can be plausible explaining factors. Authors stressed that the woman's opinion about the length of acceptable pregnancy interval is perhaps the most important predicting factor and should be considered into future research.

**Main conclusion: all studies retrieved (systematic reviews with meta-analyses and large cohort studies) failed to demonstrate a clear association between the mode of delivery and the subsequent fertility.**

## 7.2 Subsequent ectopic pregnancy

### 7.2.1 Background

An ectopic pregnancy occurs when an embryo implants outside the uterine cavity, for example in the fallopian tube. This is one of the primary causes of morbidity and mortality for pregnant women occurring in 1%–2% of all pregnancies. Several risk factors for ectopic pregnancy have been identified, including a history of pelvic inflammatory disease, previous ectopic pregnancy, previous pelvic surgery and the use of intrauterine devices.<sup>53</sup> Additionally, a large multicentre case-control study showed that previous Chlamydia trachomatis infection, previous adnexal surgery or appendectomy, in vitro fertilization and embryo transfer in women with tubal infertility were also significant risk factors for the occurrence of ectopic pregnancies.<sup>54</sup>

Although the evidence has been conflicting up to date, having a previous caesarean section has also been considered as a risk for subsequent ectopic pregnancy, without clear explaining mechanisms to support such association. However, a link with placental bed disruption, infection, or adhesion formation seems credible, themselves being potentially influenced by the indication for the caesarean section.<sup>53</sup>



### 7.2.2 Systematic reviews and meta-analyses

A systematic review and meta-analysis was published by O'Neill (2013)<sup>53</sup> to evaluate the risk of subsequent ectopic pregnancy in women with a previous caesarean section, compared with vaginal delivery. Thirteen studies were included, which recruited a total of 61 978 women. None of them reported the indication for which a caesarean section was performed. Only one study reported the reasons to opt for a caesarean section, including mainly fetal distress, failure to progress or breech presentation (81.3%).<sup>55</sup> Nevertheless, except age, no other potential confounding factors were examined in this study (e.g. history of previous pregnancy loss, history of surgery, infertility and pelvic inflammatory disease [PID]). O'Neill et al. (2013)<sup>53</sup> recognized the inherent weaknesses of the included studies hampering to draw reliable conclusions about the association under investigation (data of poor or variable quality, inadequate sample sizes and insufficient power to detect a difference, no a priori sample size calculations, no adjustment for potential confounding factors, lack of selection of an appropriate, unbiased control group, recall bias, and measurement bias). Consequently, we decided not to report the main results obtained from this systematic review.

### 7.2.3 Update with primary studies

Due to the low quality of epidemiological studies included in the above-mentioned systematic review, these authors decided to conduct a population-based cohort study, using nationwide registry data including women with a primary caesarean section to assess the likelihood of stillbirth, miscarriage, and ectopic pregnancy compared to women with a primary vaginal delivery.<sup>56</sup> This study covered the period from 1982 to 2010 in Denmark. Index live births included singleton and multiple gestation (twins or more) deliveries. In this study, women were followed up from the date of birth of the first child until the subsequent reproductive event of interest or until censoring due to live birth, death, emigration, or study end (December 31, 2010). Many confounding variables were used to adjust the statistical models but no data were available on known risk factors, including the number of previous sexual partners, history of pelvic inflammatory disease, and age at first intercourse. There were 832 996 first live births, of which 607 252 (72.9%) were SVDs, 38 950 (4.7%) were elective caesareans, and 2876 (1.1%) were maternally requested caesareans. During the study

period, there were 11 877 ectopic pregnancies, a rate of 1.4 per 100 women. When all caesareans were analysed together, a 9% increased rate of ectopic pregnancy was found (HR 1.09, 95% CI [1.04, 1.15]), yielding an absolute risk increase of 0.1% and a Number Needed to Harm of 1000 women. Taking into account the indication, an increased rate of subsequent ectopic pregnancy was found in women with a prior emergency caesarean (HR 1.09, 95% CI [1.03, 1.15]) and elective caesarean (HR 1.12, 95% CI [1.03, 1.21]). The increased rate is statistically significant but small in size and cannot be considered as a dangerously increased rate of ectopic pregnancy. Authors reported that a reduction of 0.0196 ectopic pregnancies per 100 population could be expected if women were not exposed to a caesarean delivery (Population Attributable Risk = 0.0196 per 100). For women who requested the caesarean delivery (n= 2876), 24 had an ectopic pregnancy (HR 1.02, 95% CI [0.68, 1.53]).

For the relation between ectopic pregnancy in relation with caesarean section vs. vaginal delivery, only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

The more recent population-based cohort study showed a risk increase of 9% after caesarean deliveries. The increased rate is statistically significant but small in size and cannot be considered as a dangerously increased rate of ectopic pregnancy. This study attempted to correct main methodological weaknesses and included many confounding variables to adjust the statistical models (e.g. previous ectopic pregnancy, placenta abruption or placenta praevia) but no data were available on well-known risk factors including the number of previous sexual partners, history of pelvic inflammatory disease, age at first intercourse and access to fertility services. For women followed-up for a maximum of 3 years, such increase is not more significant for caesarean deliveries.

**Main conclusion: So far, the epidemiological studies failed to definitely confirm the hypothesized association between caesarean section and ectopic pregnancy. The very small increased rate of ectopic pregnancy after caesarean section could be partly explained by underlying medical conditions.**



## 7.3 Placenta praevia, placenta accreta, placental abruption and uterine rupture

### 7.3.1 Background

The mode of delivery for the first birth can have major implications for future pregnancies. Some specific consequences can only occur after uterine surgery (e.g. presence of uterine scar and abdominal scar) or after VD (e.g. episiotomy). In these cases, it is impossible to compare outcomes between groups. The following section will discuss the potential consequences of a previous CS for future pregnancies and deliveries.

Placental complications such as placenta praevia, placenta accreta, and placental abruption often are reported to be associated with previous CS. Placenta accreta is a severe obstetric complication characterized by abnormally deep attachment of the placenta, with adherence to the myometrium rather than the endometrium.<sup>57</sup> If the placenta actually invades the myometrium, it is termed placenta increta. If it invades even further through the uterine serosa or into organs adjacent to the uterus, it is termed placenta percreta. In many circumstances, the term placenta accreta is used to describe placenta accreta, percreta and increta interchangeably as a single-disease spectrum.<sup>57, 58</sup> In women with placenta accreta, the tight adherence of the placenta to the uterine wall hampers the normal separation of the placenta from the uterus after delivery, leading to maternal haemorrhage.<sup>57</sup> Placenta accreta is possibly the most clinically significant long-term maternal morbidity after a CS and is associated with life-threatening haemorrhage that frequently results in peripartum hysterectomy.<sup>57</sup>

Uterine rupture is a rare obstetric complication associated with severe maternal and perinatal morbidity and mortality. Uterine rupture rarely occurs in women with a native, unscarred uterus but mainly in women with a uterus with a surgical scar from previous surgery (most often CS).<sup>59</sup> Uterine rupture occurs when a full-thickness disruption of the uterine wall that also involves the overlying visceral peritoneum (uterine serosa) is present. In contrast to frank uterine rupture, uterine scar dehiscence involves the disruption and separation of a pre-existing uterine scar. Uterine scar dehiscence is a more common event than uterine rupture and seldom results in major maternal or

fetal complications. Although a uterine scar is a well-known risk factor for uterine rupture, the majority of events involving the disruption of uterine scars result in uterine scar dehiscence rather than uterine rupture. These two entities must be clearly distinguished, as the options for clinical management and the resulting clinical outcomes differ significantly. However, even in high-risk subgroups, the overall incidence of uterine rupture is low. From 1976-2012, 25 peer-reviewed publications described the incidence of uterine rupture, and these reported 2 084 cases among 2 951 297 pregnant women, yielding an overall uterine rupture rate of 1 in 1 146 pregnancies (0.07%).<sup>59</sup>

### 7.3.2 Systematic reviews and meta-analyses

No systematic reviews were identified.

### 7.3.3 Primary studies

Daltveit et al. (2008) conducted a large registry study using data on births recorded in the Medical Birth Registry of Norway between 1967 and 2003.<sup>60</sup> In the analysis of women with one previous birth (n=637 497) selected complications in second pregnancy were outcomes. Women with a first CS formed the exposed group, and women with a first VD formed the reference group. In the analysis of women with two previous births (n=242 812), selected complications in third pregnancy were outcomes. Women with a CS in the first or the second birth formed the exposed groups, and women with a first and second VD formed the reference group. To evaluate possible dose-response effects of CS, women with a CS in first and second birth were also analysed. A sensitivity analysis was conducted excluding women with the selected adverse outcome in any of their previous pregnancies. These analyses were performed to adjust for confounding by indication. This will allow to exclude complications with a high recurrence risk and a high risk of CS, i.e. complications that are strongly associated with both the exposure (previous CS) and the outcome (a recurrent complication).

Maternal outcomes measured included placenta praevia, placenta accreta (from 1969 onward), placental abruption, preeclampsia and bleeding during pregnancy and uterine rupture.



Compared with a VD at first birth, a CS at first birth was followed, in a second pregnancy, by increased risks of complications. The highest OR was observed for uterine rupture (Table 2). After excluding women with the actual complication at first birth, the corresponding ORs were, in general, slightly reduced but remained significant.

Based on this exclusion, reduction in numbers of CS needed to prevent one case was estimated to be 389 (bleeding in pregnancy), 114 (preeclampsia), 1 140 (placenta praevia), 3 706 (placenta accreta), 300 (placental abruption), and 461 (uterine rupture).

**Table 2 – Adverse outcomes in second pregnancy according to mode of delivery at first birth among women with two or more single births**

Outcome 2 <sup>nd</sup> pregnancy	Mode of 1 <sup>st</sup> Delivery		
	Vaginal (%) **	Caesarean (%) **	OR <sup>£</sup> (95% CI)
<b>Bleeding in pregnancy</b>			
All women (637 497)	2.75	2.83	1.1 (1.0 – 1.1)
Selected women*	2.64	2.65	1.1 (1.0 – 1.1)
<b>Preeclampsia</b>			
All women (637 497)	1.60	5.04	2.9 (2.8 – 3.1)
Selected women*	1.28	2.43	1.7 (1.6 – 1.8)
<b>Placenta praevia</b>			
All women (637 497)	0.22	0.36	1.5 (1.3 – 1.8)
Selected women*	0.22	0.33	1.4 (1.2 – 1.7)
<b>Placenta accreta</b>			
All women (637 497)	0.03	0.07	1.9 (1.3 – 2.8)
Selected women*	0.03	0.06	1.9 (1.3 – 2.8)
<b>Placental abruption</b>			
All women (637 497)	0.48	0.97	2.0 (1.8 – 2.2)
Selected women*	0.48	0.84	1.7 (1.6 – 1.9)
<b>Uterine rupture</b>			
All women (637 497)	0.006	2.0	37.4 (24.9 – 56.2)
Selected women*	0.006	0.20	37.2 (24.7 – 55.9)

Note: \* Selected women: women without actual outcome at first birth (These analyses were performed to adjust for confounding by indication); £ adjusted for maternal age and year of birth; Source: Daltveit et al. (2008)<sup>60</sup> \*\* In the original publication data were given per 1000. For easier comparability we converted them to percent.



In third births, ORs after repeat CS were similar to or lower than the ORs after one CS; also here, the exclusion of women with the actual outcome in any of their previous pregnancies tended to reduce the ORs. This study also shows those adverse outcome in a third pregnancy, depending on whether it was preceded by 2 VD, one VD and one CS (depending on the order) or 2 CS. Those data can be found in the supplement (Appendix 4, Table 8).

The relationship between repeat CS and placenta accreta was studied in a multicentre cohort of 30 132 women in the American Maternal Fetal Medicine Units (MFMU) Network who underwent CS delivery without labour.<sup>61</sup> In women having their first CS, the rate of placenta accreta was 0.24%. The rate increased to 0.31% (OR 1.3; 95% CI [0.7, 2.3]), 0.57% (OR 2.4; 95% CI [1.3, 4.3]), 2.13% (OR 9.0; 95% CI [4.8, 16.7]), 2.33% (OR 9.8; 95% CI [3.8, 25.5]) and 6.74% (OR 29.8; 95% CI [11.3, 78.7]) in women having their second, third, fourth, fifth, and sixth CS deliveries, respectively. Note that these rates are much higher than in the Norwegian study by Daltveit et al. It is unclear whether this corresponds to other definitions used or whether there are other reasons.

In the MFMU cohort, the most common surgical complication associated with placenta accreta was cystotomy, which was noted in 15.4% of the patients with placenta accreta. In this large cohort study, multiple CS were also associated with an increased risk of hysterectomy, cystotomy, bowel injury, ureteral injury, ileus, blood transfusion of at least 4 U, need for postoperative ventilation, intensive care unit admission, increased operative time, and increased hospital stay. Other morbidity, including wound dehiscence, deep venous thrombosis, pulmonary embolus, the need for reoperation, and death, was not increased in women with increasing number of CS deliveries.

A large registry based retrospective cohort analysis in the US (n=20 095) based on birth and hospital registries was published by Lydon-Rochelle et al. (2001).<sup>62</sup> This study focussed on uterine rupture during VD among women with a prior CS delivery. Approximately 60% of women with a previous CS tried labour in a subsequent pregnancy. These authors separated different initiations of labour: spontaneous onset of labour, induced labour by prostaglandins and induced labour by other means. These three groups of labour were compared with subsequent caesarean

delivery without labour. Uterine rupture occurred at a rate of 1.6 per 1000 among women with repeated CS without labour (11 women), 5.2 per 1000 among women with spontaneous onset of labour (56 women, RR 3.3, 95% CI [1.8, 6.0]), 7.7 per 1000 among women whose labour was induced without prostaglandins (15 women, RR 4.9, 95% CI [2.4, 3.7]), and 24.5 per 1000 among women with prostaglandin-induced labour (9 women, RR 15.6 95% CI [8.1, 30.0]). For women with one prior CS, the risk of uterine rupture is higher among those with a VD, especially when labour is induced. Labour induced with a prostaglandin confers the highest risk.

In a large Norwegian study using a historical cohort design, CS was associated with a moderately increased risk of placenta praevia, placenta accreta and placental abruption and a highly increased risk of uterine rupture in a subsequent pregnancy. Excess risks were reduced after excluding women with the actual complication in any of their previous births, to adjust for confounding by indication. To obtain less biased effects of CS on subsequent pregnancies, it is important to take into account obstetric history. Importantly, the timing of the CS was not reported, and it is impossible to differentiate CS performed before the labour from other situations. It was previously shown that a trial of labour at the second delivery after a previous caesarean delivery was associated with a significant increase in the risk of uterine rupture especially when labour is induced.

A large prospective observational study was conducted in 19 US academic centres (MFMU) over 4 years (1999-2002), aiming to estimate the magnitude of increased maternal morbidity associated with increasing number of caesarean deliveries. Authors confirm that serious maternal morbidity increases with increasing number of CS. The major risk is attributable to that associated with placenta accreta and/or the need for hysterectomy. Women having their fourth or more CS had a 9- to 30-fold increased risk of placenta accreta and a 4- to 15-fold higher risk of hysterectomy. However, the rates for placenta accreta in this study are much larger than in the Norwegian study for unclear reasons.



**Main conclusion: caesarean delivery is associated with an increased risk of placenta praevia, placenta accreta and placental abruption and a highly increased risk of uterine rupture in a subsequent pregnancy especially when labour is induced.**

## 8 SHORT-TERM OFFSPRING OUTCOMES

### 8.1 Neonatal mortality

#### 8.1.1 Background

The neonatal mortality refers to the number of neonatal deaths per 1000 live births, a neonatal death being defined as a death that occurs during the first 28 days of life (0-27 days).

#### 8.1.2 Systematic reviews and meta-analyses

The systematic review performed for the development of the NICE guideline on CS (2004 updated in 2012) identified two cohort studies comparing the neonatal mortality in planned CS compared with planned vaginal birth for women with an uncomplicated pregnancy and no previous CS.<sup>17, 63</sup>

Dahlgren et al. (2009) conducted a population-based cohort study of deliveries between 1994 and 2002 that included healthy nulliparous women who had undergone elective pre-labour CS (using breech presentation as a surrogate) with those in women who had undergone spontaneous labour with anticipated vaginal delivery (VD) at full term.<sup>20</sup> There were 1 046 deliveries in the pre-labour CS group and 38 021 in the VD group. In this cohort there were 5 580 unplanned CS in the planned VD group (14.7%). Among those 1 046 who had a planned CS (for breech delivery), a mortality risk of 0/1046 (0 per 1000 live births) was reported compared with a mortality risk of 38/38 021 (1 per 1000 live births) in the planned vaginal birth group (non breech). Breech deliveries were used as a way to assure that women undergoing CS would be similar to the vaginal delivery group by eliminating selection bias due to the fact that a CS was deliberately chosen. The same study showed similar results for other severe neonatal outcomes: hypoxic-ischemic encephalopathy (2/1046 or 0.2% in CS vs. 89/38 021 in VD; RR 0.81; 95% CI [0.22, 3.00]), intracranial haemorrhage (0/1046 or 0% in CS vs. 10/38 021 or 0.01% in VD), neonatal respiratory morbidity (126/1046 or 12% vs 4 .383/38 021 or 11.5%; RR 1.04; 95% CI [0.88, 1.23]). The evidence for all outcomes was of very low quality and not statistically significant.



Mac Dorman et al. (2008) examined neonatal mortality risk by method of delivery for low-risk women.<sup>64</sup> In this registry study, low-risk births were singleton, term (37-41 weeks' gestation), vertex births, with no reported medical risk factors or placenta praevia and with no prior caesarean section. All US live births and infant deaths for the 1999 to 2002 birth cohorts (8 026 415 births and 17 412 infant deaths) were included. There were 271 179 deliveries in the CS group and 7 755 236 in the VD group. Using the intention-to-treat methodology, a "planned vaginal delivery" category was formed by combining vaginal births and CS with labour complications or procedures since the original intention in both cases was presumably a vaginal delivery. This group was compared with CS with no labour complications or procedures, which is the closest approximation to a "planned caesarean delivery" category possible, given data limitations. A mortality risk of 469/271 179 (1.73 per 1000 live births) in the CS group and 5 546/7 755 236 (0.72 per 1000 live births) in the VD group were calculated (RR 2.4; 95% CI [2.20, 2.65]). In the most conservative model, the adjusted odds ratio for neonatal mortality was 1.69 (95% CI [1.35, 2.11]) for caesarean sections with no labour complications or procedures, compared with planned vaginal deliveries. Adjustments were made for a number of factors, such as gestational age, age of the mother, education and smoking.

### 8.1.3 Update with primary studies

A different approach was used by Xie (2015),<sup>6</sup> who analysed data for 31 high-income industrialized countries in 2010 (or the nearest year) obtained from the World Health Organization, Organization for Economic Cooperation and Development, World Bank, and individual countries. The CS delivery and infant mortality rates varied among the included countries: from 15.6 to 50.0 percent and from 1.9 per to 6.8 per 1 000 live births, respectively. They found that CS delivery rates were positively correlated with infant mortality rates (Pearson correlation coefficient: 0.41,  $p < 0.05$ ) after adjustment for maternal age, infant sex, per capita GDP, and the Gini index, i.e. a measure of the distribution of wealth within the population ( $p < 0.03$ ). The association however disappeared after further adjustment for preterm birth ( $p = 0.07$ ).

For the relation between neonatal mortality in relation with caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

The systematic review of two large observational studies, and also an ecological study in 31 high-income countries give inconclusive results for the association between CS and neonatal mortality, but the situations were somewhat different between studies. The first population-based cohort study showed no significant difference in mortality, but was grossly underpowered. The ecological study reported no significant correlation between planned CS and infant mortality after adjustment for a number of risk factors. But as the infant mortality figures used are overwhelmingly dominated by preterm births and by specific causes (malformations, intrauterine infections...), any effect on low-risk, term births is masked. In conclusion, only the large registry study is of use for our research question. Still, despite the adjustments for a number of relevant risk factors, there remains a risk of residual confounding and selection bias, as an unknown percentage of these planned CS may have been carried out for reasons linked to the risk of neonatal mortality.

**Main conclusion: there is conflicting crude evidence and no evidence of a causal association between neonatal mortality and mode of delivery.**

## 8.2 Neonatal respiratory problems

### 8.2.1 Background

It has long been suspected that infants delivered by elective CS may be at increased risk of neonatal respiratory morbidity and that this risk is related to gestational age (GA) at birth.<sup>65</sup> Possible consequences of respiratory morbidity are admission to neonatal intensive care units, separation of mother and child (hampering bonding and the onset of breastfeeding), need for respiratory support, painful procedures, treatment with antibiotics and mechanical ventilation as well as the risk of severe complications. The timing of an elective CS consistently shows an increased risk of respiratory morbidity with decreasing GA, but results from studies that compare the



neonatal outcome of elective CS with other modes of delivery are less clear.<sup>66</sup>

### 8.2.2 Systematic reviews and meta-analyses

In 2007, Hansen et al. conducted a systematic review to assess this relationship between delivery mode by elective CS vs. VD or intended VD.<sup>66</sup> Nine primary studies were included (one case-control and eight observational studies including one prospective cohort study). Studies include outcomes such as respiratory distress syndrome (RDS), but also transient tachypnea of the newborn (TTN), persistent pulmonary hypertension and overall respiratory morbidity. All those studies concerned near-term born babies (37 weeks GA and more).

All studies found that delivery by elective CS was associated with an increased risk of various respiratory morbidities in near term newborns compared with vaginal delivery although the findings were not statistically significant in all of the studies.

Four studies compared RDS in elective CS vs. (intended) VD. For RDS the overall incidence in term newborns was 0.1 – 0.2% in babies born with VD or intended VD and 0.2 – 0.7% in babies born by elective CS. In a large cohort study a seven-fold risk increase (OR 7.1; 95% CI [2.6, 19.3] adjusted for gestational age (GA)) was noted for babies born through elective CS compared to babies born through (intended) VD.<sup>67</sup> One other study also found an increased risk (OR 5.9; 95% CI [2.3, 32.4]) matched by GA, while the two other studies looking at this comparison report an increased risk point estimate which was not statistically significant.

Six studies compared TTN in elective CS vs. (intended) VD. For TTN the overall incidence in these studies was 0.3 – 3% in infants delivered through VD against 0.9 – 12% for infants delivered through elective CS. A significant 2 to 3 fold increase was found in three of those studies. Adjustment for GA was made in two of the studies. The three other studies also showed an increased point estimate without, however, reaching statistical significance. Also for other and overall neonatal respiratory problems this systematic review found systematically higher risks for those infants born through (elective) CS. But again, those were all observational studies. The authors felt it was inappropriate to perform a meta-analysis with a pooled risk estimate because of the methodological differences between the studies.

The overall risk for respiratory morbidity, however, was found to increase about 2 to 3 times, though some studies presented much higher risk estimates. A decreasing risk with increasing GA was shown in two studies. The authors conclude that delivery by elective CS was shown to increase the risk of respiratory morbidity in all studies eligible for inclusion. The magnitude of this relative risk seemed to depend on gestational age even in deliveries after 37 completed weeks of gestation.

### 8.2.3 Update with primary studies

In 2008 the same research group published a cohort study (not included in the previous SR) on the same subject including babies delivered between 1998 and end of 2006 with GA between 37 and 41 weeks in the Aarhus (Denmark) birth cohort (n = 34 458).<sup>68</sup> The reported results are basically similar to the results of the previous SR.

The overall frequency of respiratory morbidity was 1.8% with 0.2% having serious respiratory morbidity. In the low risk pregnancy population this frequency was only slightly lower (see supplement for details; Appendix 4, Table 8). Also after adjustment for several confounders, the risks for respiratory morbidity were higher in infants delivered through elective CS than those delivered through (intended) VD. However, the relative risk increased with decreasing GA. Many comparisons are reported in this publication (see supplement for details on the analyses; Appendix 4, Table 8). The OR for serious respiratory morbidity (not adjusted for confounders because of the small number of observations) and comparing to intended VD in a sub-group of low risk pregnancies were for elective CS: OR 3.2 (95% CI [0.8, 1.3]) at 37 weeks, 4.2 (95% CI [1.6, 11]) at 38 weeks and 2.7 (95% CI [0.5, 14]) at 39 weeks. Similar patterns were recorded for all respiratory morbidity and for all pregnancies. In an additional analysis on all pregnancies but taking intended VD at 40 weeks as a reference the differences for serious respiratory morbidity were even more apparent: for elective CS at 37 weeks an OR of 13.6 (95% CI [5.1, 36]), at 38 weeks OR 6.0 (95% CI [2.8, 13]) and at 39 weeks OR 1.3 (95% CI [0.0, 5.1]) Interestingly, this study also included information on elective CS on maternal request for a subgroup of births (788 women between 2002 and 2006). The outcome results for this group were similar to the group of women with a low-risk pregnancy. The authors conclude that, if possible, it is preferable to



postpone an elective CS until 39 weeks GA to avoid neonatal respiratory morbidity.

For the relation between neonatal respiratory problems in relation with (elective) caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

In a systematic review, all off nine observational studies give an indication of an increased risk of between two-fold to seven-fold increased risk for neonatal respiratory problems. However, not all of those individual studies reached statistical significance and due to large heterogeneity in methods the authors of this systematic review found it unwise to conduct a meta-analysis.

In a Danish cohort study, a similar association was found: increased risk in infants born near-term through elective CS vs. those born through (intended) vaginal delivery but with an increasing risk ratio with decreasing gestational age (especially at GA 37 and 38 weeks).

Also in the studies showing an association, the causal nature of any association is difficult to prove in those observational studies because of the high risk of residual confounding.

**Main conclusion: there is observational evidence of an association between neonatal respiratory problems and (elective) caesarean section. To avoid neonatal respiratory morbidity, it is preferable to postpone an elective CS until 39 weeks gestational age if possible.**

## 8.3 Cerebral palsy

### 8.3.1 Background

Cerebral palsy (CP) is a group of clinical syndromes more or less severe. Signs vary among affected patients but they often include abnormal muscle tone (spasticity or weak muscles), poor members' coordination and tremors. Addition characteristics include problems with vision, hearing, swallowing, sensation and speaking. These conditions are due to abnormal development or damage to the parts of the brain that control movement, balance, and posture.

There is some evidence that intrapartum factors may cause CP, i.e. intrapartum hypoxia, or brain damages caused by antenatal infection (e.g. toxoplasmosis or rubella). Cerebral palsy may also have its origin in postnatal events, especially Hypoxic Ischemic Encephalopathy (HIE) and prematurity-related problems (in very low birth weight and very preterm infants, i.e., gestational age < 28 weeks or <25 weeks).

The prevalence of cerebral palsy has been remarkably stable for decades (around 1.5-2.5/1000 live births), with little or no variation among western nations.<sup>69</sup> This has not been the case among very low birth weight and very preterm infants, among whom prevalence increased after the introduction of neonatal intensive care that allow extremely low gestational age neonates to survive.

Fear of cerebral palsy (CP) litigation has a major influence on the defensive decision-making of the obstetrician to perform a CS, convinced this could offer a protective effect.



### 8.3.2 Systematic reviews and meta-analyses

In the SR and MA from O'Callaghan et al. (2013), nine case-control and four cohort studies were included in the overall analysis.<sup>70</sup> A systematic search through the usual databases was made up to December 2012. This SR and MA only included confirmed cases of CP. In total this MA included 3 810 cases and 1 692 580 controls.

Meta-analysis showed no overall association of all CS with CP (OR 1.29; 95% CI [0.92, 1.79] for CS vs. VD). Emergency CS was associated with an increased risk of CP (OR 2.17; 95% CI [1.58, 2.98]) whereas there was no significant association between elective CS and CP (OR 0.81; 95% CI [0.41, 1.58]). However, the indication for the CS was not registered; hence, this association between emergency CS and VD might be caused by selection bias. However, when considering newborns born at-term and preterm newborns there was a statistically significant association in the born at-term infants (increased risk CS vs. VD): OR 1.6 (95% CI [1.05, 2.44]), while in preterm born children there was no significant association (OR 0.81, 95% CI [0.47, 1.40]). Again, no information was given on the indication of the CS, and no distinction was made between elective and emergency CS, making these results uninterpretable.

According to the authors, there is a likely confounding that acute or chronic fetal compromise will often precipitate the CS intervention. The results should be interpreted with caution, in the meta-analysis the unadjusted OR were used and therefore there is no adjustment for confounding. The overall conclusion is that this literature review does not support the use of elective or emergency CS to prevent cerebral palsy.

### 8.3.3 Update with primary studies

Of 11 publications retrieved, one was retained for a full text assessment.<sup>71</sup> This ecological study by Racinet et al. (2015) reported the relation between CS for fetal indications and CP in one French county (Département de l'Isère) over the years 1997 – 2002. We discarded it as invalid because it was purely an ecological study that compared CS rates for fetal indications and CP prevalence and it did not include elective CS for non-medical reasons.

For the relation between cerebral palsy and caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

**Main conclusion: the evidence does not support an overall increase or decrease in the risk of cerebral palsy with CS. The literature review does not support the use of CS to prevent cerebral palsy in uncomplicated, term pregnancies with babies in cephalic presentation.**



## 9 LONG-TERM OFFSPRING OUTCOMES

### 9.1 Immune disorders

#### 9.1.1 General background

Caesarean section (CS) delivery has long been suspected to have an influence on the development and function of both innate and acquired immunity, and the ensuing risk of disease. The association between CS and immune diseases was explored in many epidemiological association studies. A review of many of those observational studies was made by Cho et al. (2013).<sup>72</sup> Outcomes related to immune disorders include later risk for asthma, diabetes mellitus type 1, atopy and gastrointestinal diseases.

The mechanisms through which caesarean section could impact the development of the immune system are largely hypothetical but may be at the level of the intestine by altering bacterial colonization or may be related to an adverse birth stress response and epigenetic modification of gene expression in the immune system.<sup>72</sup>

However, this has only been investigated in observational studies that have a high risk of bias since adjusting can only be performed for measured confounding factors and many do not differentiate between elective caesarean sections for medical or non-medical reasons and for emergency sections. Therefore, observed associations may be spurious.

Some of the studies concern only one disease while other studies are dealing with multiple outcomes. Study design and description will therefore not be repeated for each outcome but we will refer to the appropriate section where needed.

#### 9.1.2 Asthma

##### 9.1.2.1 Background

In 2008 a meta-analysis including 20 studies indicated that CS is suspected to increase asthma in children (<18 years) compared to VD (OR 1.20; 95% CI [1.14, 1.26]).<sup>73</sup> A similar association was detected when also including three studies of asthma at any age, but as important study heterogeneity was observed, the authors were less certain about this result. This study also has a large risk of bias due to heterogeneous designs, large heterogeneity in the data, unmeasured confounding and recollection bias (parental questionnaires). Moreover, this meta-analysis did not consider the reason of CS (elective or emergency and medical or non-medical reason).

##### 9.1.2.2 Systematic reviews and meta-analyses

In 2015, a large meta-analysis (search date 2013) assessed the risk of asthma in children born by CS vs. VD with a distinction between elective (pre-labour) or emergency CS and normal or instrumental VD.<sup>74</sup>

After the selection of the most relevant papers that fitted the eligibility criteria (diagnosis of asthma during childhood and stratifying results with specific delivery method, 26 cohort studies were included, of whom 15 were retrospective and 11 prospective. The majority of studies (20/26) were done out in Europe (Denmark, Finland, Norway, Scotland, Sweden, The Netherlands and UK). Three studies were conducted in the US, one in New Zealand and one in Korea. One Danish study included participants who were diagnosed before age of 28. The outcome 'asthma' was in some studies diagnosed by a physician, but was self-reported in other studies. Summary effect estimates were calculated by using random-effects models.

The results showed an increased risk of asthma for all CS compared to VD (OR: 1.16; 95% CI [1.14, 1.19]; 26 studies) and also after stratification for elective CS only (OR 1.21; 95% CI [1.17, 1.25]; 9 large European studies). The association did not significantly differ in sensitivity analyses, stratifying for study design (prospective vs. retrospective, year of publication, outcome definition (physician diagnosis of asthma vs. other), age of diagnosis (<10



years,  $\geq 10$  years)). A small positive association was also found for instrumental VD vs. normal VD (7 studies; summary OR 1.07; 95% CI [1.04, 1.11];  $I^2=54.9\%$ ).

This meta-analysis included prospective and retrospective cohorts, including some very large registry cohorts from Scandinavian countries and the UK. Nevertheless, the term elective CS is not equal to a non-medical reason but to “a planned CS performed for either maternal or fetal indications before the onset of labour”.<sup>74</sup> We consider the quality of the evidence from this meta-analysis as low (Amstar 6/11) due to the heterogeneous study designs with different outcome definitions and the high risk for confounding bias due to poor adjustments.

The authors conclude that children delivered by elective CS and emergency CS have about 20% increased risk to develop asthma in childhood compared to VD. The authors recognize that “the exact mechanisms underlying this association of CS and offspring’s asthma without the effect of indications need further investigation in children born by CS on maternal request”.<sup>74</sup>

### 9.1.2.3 Update with primary studies

From the 187 articles retrieved, 112 were published in 2013-2016 and three were retained.<sup>75-77</sup> Three additional publications were found through hand searching.<sup>78-80</sup> However, the publication by Wu et al. (2016) considered multiple risk factors for developing asthma, including the mode of delivery. Although this analysis showed CS to be one of the risk factors for developing asthma we decided to discard this study because there was no specific subgroup analysis on the mode of delivery.

Therefore, five recent retrospective cohort studies, not included in the meta-analysis of Huang et al. (2015) were retained after the selection and the quality appraisal of retrieved papers:

1. The largest of these is a Danish cohort study by Sevelsted et al. which is a well conducted study but due to its observational design only gives evidence of moderate quality.<sup>77</sup> This study aims to investigate the association between CS (all types) and the development of numerous

immune diseases, such as asthma, allergy, inflammatory bowel disease, and type 1 diabetes. This is a large registry study with data from Danish national registries.

The Danish Medical Birth Registry records all live births in Denmark since 1973. For this study children born between 1973 and 2012 were included. Measured confounders were gender, parity, birth weight, attained age at diagnosis, calendar time of birth, season of birth, maternal age and maternal illness (for the disease in question). The researchers restricted the large population to mature children and excluded from analyses premature children (defined as birth weight below 2500 g) and children with missing information on birth weight or other confounders (final  $n=1.9$  million of children, i.e. 80% of total number of births). Cases were identified through the use of ICD-8 and ICD-10 codes from the Danish National Patient Registry that was established in 1977, recording all in-patient discharges since 1977 and outpatient admissions since 1994. The study population was followed-up from 1977 to 2012 for a total of 23 million person years in the age range 0 to 15 years. Approximately 14% of the study population was delivered by CS and 103 822 children (5.5%) were diagnosed with asthma (48 858 diagnosed at age  $> 5$  year (2.6%)).

The effect of CS delivery on childhood disease incidences was estimated by means of confounder-adjusted incidence rate ratios with 95% confidence intervals obtained in Poisson regression analyses. After adjusting for maternal and infantile confounders, children delivered by CS had significantly increased adjusted incidence rate ratio (aIRR) for asthma (1.23; 95% CI [1.21, 1.25]). When the analysis was limited to children older than 5 years at the first contact, results did not differ substantially (aIRR 1.16; 95% CI [1.13, 1.19]). This sensitivity analysis was performed because in older children, the diagnosis is more robust. It is important to stress that no distinction was made according to the indication of the CS or the timing of the CS delivery (elective or in emergency). The proportion of CS was significantly higher ( $\chi^2$ ) for mothers with immune disorders (i.e. asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease, diabetes type 1, immune deficiencies, psoriasis, and coeliac disease) compared to the proportion in women without those diseases. Interestingly, for mothers



with (a history of) leukaemia the proportion of mothers delivering through CS is significantly lower, although this might be a chance finding ( $p=0.0106$ ). Especially mothers with type 1 diabetes had an increased risk of caesarean delivery compared with mothers without diabetes type 1 (27% vs. 14%).

2. The same research team conducted a subsequent study.<sup>79</sup> One of the aims of this study was to analyse the risk of developing asthma after CS with or without the rupture of membranes to test the hypothesis that CS delivery could mediate the asthma risk through alterations of the newborn's microbiome. In this publication two data sources were used: The Copenhagen Prospective Studies on Asthma in Childhood<sub>2000</sub> (COPSAC2000) and a combination of several Danish national registries.

The COPSAC<sub>2000</sub> population consists of a high-risk birth cohort of 411 children born 1998-2001 to mothers with a history of asthma. Asthma was diagnosed in children prospectively by physicians using strict standardised diagnostic criteria. Following this definition, 18% (72 children) developed asthma before the age of 7 years. The delivery by CS or VD was recorded as a dichotomous variable: 87 children (22%) were delivered by CS. In this high risk cohort, a significant association between CS and development of asthma was found with a confounder adjusted HR of 2.18 (95% CI [1.27, 3.73]).

From the Danish Medical Birth Registry, data of all live births from 1997-2010 were selected. Data on all confounders were available for 864 049 (95%) children (age 0-15 years). Confounders were gender, parity, birth weight, gestational age, maternal age, multiple births, mother's use of antibiotics during pregnancy, maternal employment and education (those two last confounders were obtained from Statistics Denmark). Caesarean delivery was classified as: (1) elective CS before delivery; (2) emergency CS because of delivery complications performed during delivery; (3) emergency CS because of pregnancy complications performed during delivery; and (4) emergency CS performed before onset of labour. Combinations of groups allowed to dichotomise the exposure between either CS performed before rupture of membranes (1 and 4) or CS performed after rupture of membranes (2 and 3).

During the period 1997 - 2010, 19% (163 462) of the Danish children were born by CS. Ten percent (87 559) of the children were born by CS performed before rupture of membranes (71% elective and 29% emergency before delivery), 9% (75 863) of the children were born by CS performed after rupture of membranes (88% emergency because of delivery complications, 12% emergency because of pregnancy complications). Asthma was evaluated based on long-term recurrent consumption of inhaled corticosteroids: at least 200 defined daily doses filled at a pharmacy. Following this definition, 38 085 (4.4%) of the children were classified as having asthma. In sensitivity analyses two alternative definitions of childhood asthma were used: 1) asthma hospitalizations based on ICD-10 data from the Danish National Patient Registry 2) outpatient care for asthma for minimum 1 year based on data from the same registry.

In this large registry study, the association between type of delivery found in the COPSAC<sub>2000</sub> cohort was confirmed, but with a smaller effect size: aIRR 1.16 (95% CI [1.13, 1.19] in the model with the largest correction for confounding. The main confounder was prematurity. A higher risk for asthma was found for CS performed before rupture of membranes (aIRR vs. vaginal delivery 1.20; 95% CI [1.16, 1.23]) compared with CS performed after rupture of membranes (aIRR vs. vaginal delivery 1.12; 95% CI [1.09, 1.16]). Sensitivity analyses were conducted on children above 6 years of age at diagnosis and using the variable outcome definitions described above, all leading to similar results. Authors confirmed CS to be a risk factor for childhood asthma, which is more pronounced when CS is performed before rupture of the membranes.

3. The study by Kristensen et al. is a population- and registry-based cohort study based on all children born in Denmark from January 1997 through December 2012 and based on the same Danish registries as the two previous studies.<sup>78</sup> Its aim was to explore the associations between emergency vs. elective CS and disease associated with immune function in the offspring. Numerous outcomes were evaluated: asthma, laryngitis, gastroenteritis, ulcerative colitis, Crohn and coeliac disease, respiratory tract infection, juvenile idiopathic arthritis and cancer. Birth data were obtained from the Danish National Birth Registry and



diagnostic data (based on ICD-10 codes) were obtained from the Danish National Patient Registry.

Among the 1 031 424 children born during that period, 790 569 children aged 0 to 14 years were included in the study sample. Of these, 63 811 (8.1%) were born by elective CS, and 60 319 (7.6%) were born by emergency CS. Children were followed from the day of birth to an outcome of diagnosis, emigration, death, or December 31, 2012. Hazard ratios for diseases associated with immune function in children delivered by emergency and elective CS with vaginal delivery as the reference were calculated by using Cox regression. All analyses were adjusted for gestational age, sex, birth weight, maternal age, maternal smoking during pregnancy, and complications during pregnancy (preeclampsia, eclampsia, haemorrhage, and hyperemesis). Globally, 45 437 (5.7%) children were diagnosed with asthma. A higher risk for asthma was found after an elective CS (HR 1.24; 95% CI [1.20, 1.28]) than after an emergency CS (HR 1.06; 95% CI [1.02, 1.10]) both compared with VD.

4. The study by Black et al. is a registry based population-based retrospective cohort study conducted in Scotland aiming to examine the relationship between planned CS and offspring health problems or death in childhood.<sup>75</sup> The following outcomes were explored: asthma, obesity, inflammatory bowel disease, type 1 diabetes, cancer and death. The study sample included data on 321 287 at-term first-born singletons born between 1993 and 2007 and followed-up until February 2015. Asthma was captured by two outcomes, either 'asthma requiring hospitalisation' or 'salbutamol inhaler prescription at age 5 years'. For the risk of asthma requiring hospital admission the full cohort was used while for the outcome of salbutamol inhaler prescription a smaller cohort starting in 2004 was used.

Asthma requiring hospital admission was slightly higher in children born through planned CS vs. unscheduled CS: 3.73% vs 3.41% (difference 0.32%; 95% CI [0.21%, 0.42%]) but this difference disappeared after adjustment for confounders (aHR 1.00, 95% CI [0.90, 1.12]). The adjusted HR compared to VD was 1.22 (95% CI [1.11, 1.34]) compared with VD. Salbutamol inhaler prescription at age 5 years was also more

likely following planned CS compared with VD (10.34% vs. 9.62%; difference, 0.72% [95% CI 0.42%, 1.01%]; adjusted HR 1.13, 95% CI [1.01, 1.26]). Nevertheless, in complete-cases analyses (a method to exclude missing data), the difference in risk of asthma requiring hospital admission (HR 1.05; 95% CI [0.91, 1.22]) and the difference in the risk of salbutamol inhaler prescription at age 5 years (HR 1.11; 95% CI [0.97, 1.27]) was no longer significant. The HR were adjusted for salbutamol prescription, maternal age, gestation at birth, maternal Carstairs deprivation score, maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks.

5. Finally, a much smaller population-based prospective cohort study conducted among 6 128 children in The Netherlands (age <7 years) aimed to test the associations of specific modes of delivery with wheezing patterns, asthma, airway inflammation and airway resistance.<sup>76</sup> Mode of delivery was categorized as (1) vaginal delivery, (2) forceps- or vacuum-assisted delivery and (3) caesarean section delivery, which was subsequently categorized into (3a) elective caesarean and (3b) emergency caesarean section delivery. Information about wheezing in the previous 12 months was collected at ages 1, 2, 3, 4 and 6 years with questionnaires based on the International Study on Asthma and Allergy in Childhood. Information on ever physician-diagnosed asthma was reported by a questionnaire at 6 years. Relevant covariates were recorded including maternal age, pre-pregnancy body mass index (BMI), educational level, parity, history of asthma or atopy and pet keeping, maternal psychological distress, maternal smoking during pregnancy, gestational diabetes, pre-eclampsia and pregnancy-induced hypertension. Information on child's sex, ethnicity, gestational age at birth and birthweight was also available.

Of all included children, 72.9% were born by a vaginal delivery, 14.2% by a forceps- or vacuum-assisted delivery, 5.2% by an elective caesarean section and 7.8% by an emergency caesarean section delivery. No differences in the prevalence of asthma were observed between children born by a caesarean section (6.9%) and children born by a vaginal delivery (6.1%). This study did not observe a statistically significant association between all kinds of CS with asthma (OR 1.09, 95% CI [0.76, 1.55]) nor between elective CS and asthma (OR 0.89;



95% CI [0.52, 1.52] or between emergency CS and asthma (OR 1.26; 95% CI [0.81, 1.95]). However, they did report an increased risk for early and persistent wheezing up to school age.

For the relation between asthma in the offspring in relation with caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

The meta-analyses of those observational studies, and also the more recent large retrospective registry cohort studies show an association of around 20% increased risk for asthma in children born through caesarean section than through vaginal delivery. A much smaller Dutch prospective study based on questionnaires did not find a statistically significant association. Those observational studies indicate that this increased risk might be higher after elective surgery compared to non-elective surgery, but the term elective caesarean section is ill-defined and used differently in several studies.

The causal nature of this association is difficult to prove with those observational studies, so there is low quality evidence that (elective) caesarean section is causal to increase the risk for the later development of asthma in the offspring.

**Main conclusion: in observational studies an increased risk for developing asthma during childhood of about 20% is reported but there is little proof of causality. The association of the development of asthma appears to be larger after elective CS than after emergency CS.**

### 9.1.3 Respiratory infections

#### 9.1.3.1 Background

In the literature there have been indications that CS compared to VD might be associated with an increased risk for respiratory infections especially in the newborn but also at later ages.<sup>68, 81</sup>

#### 9.1.3.2 Systematic reviews and meta-analyses

No systematic review or meta-analysis was found.

#### 9.1.3.3 Update with primary studies

Several of the previously cited studies on asthma also dealt with other immune disorders that might be linked with CS vs VD.

The previously described Danish cohort study (see section 9.1.2. on asthma) showed that children (age <15 years) delivered by both emergency and elective CS had an increased risk of laryngitis. Moreover, children delivered by elective CS had an increased risk of lower respiratory tract infection.<sup>78</sup> Adjusted hazard ratios for laryngitis comparing elective CS vs. VD were 1.19 (95% CI [1.14, 1.25]) and slightly lower for emergency CS vs. VD: 1.14 (95% CI [1.09, 1.2]). For pneumonia and lower respiratory tract infections those aHR were 1.20 (95% CI [1.16, 1.24]) and 1.01 (95% CI [0.97, 1.04]) respectively.

Another Danish cohort study using the same database as the previous study focused specifically on the risk of hospitalization for Respiratory Syncytial Virus (RSV) infection in children during the first 2 years of life.<sup>81</sup> A total of 399 175 children were included in this study, after excluding 28 224 children with chronic disease present at birth, including children with congenital malformations. In this cohort, 10 758 hospitalizations for RSV infection were recorded. The results show that delivery by elective CS vs. VD is associated with an increased risk of hospitalization for RSV infection. Adjusted hazard ratios for hospitalization for RSV infection were 1.27 (95% CI [1.19, 1.36]) for elective CS vs. VD. For non-elective CS vs. VD, this ratio was 1.09 (95% CI [1.01, 1.17]).

In Scopus (1<sup>st</sup> March 2016), two recent publications were retained: Magnus et al. and Moore et al.<sup>82, 83</sup>

1. In the prospective cohort study from Magnus et al. (also included in the meta-analysis on asthma outcomes), 37 171 children were followed up to 36 months within the Norwegian Mother and Child Cohort Study. Generalized linear models were used in the multivariable analysis. No association was found between CS delivery overall, or specifically elective CS and lower respiratory tract infections before 36 months of age compared to VD.<sup>82</sup>



2. In an Australian retrospective cohort study using registry data by Moore et al., 212 068 children born at-term were analysed.<sup>83</sup> The outcomes studied were bronchiolitis and pneumonia in children aged < 12 months and in children aged 12-23 months. Of those children 33 421 (16%) were delivered through elective CS. Compared to VD those children had an increased risk of admissions for bronchiolitis at age <12 months (IRR 1.11, 95% CI [1.01, 1.23]), but at age 12-23 months this result was no longer statistically significant (IRR 1.20, 95% CI [0.94, 1.53]). No association between elective caesarean delivery and number of pneumonia admissions was observed at neither age.

For the relation between respiratory infections in the offspring in relation to caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent. Results from those observational studies are conflicting.

No meta-analysis or systematic review for respiratory infection outcomes was found. A large Danish registry study shows an association of around 20% increased risk for laryngitis and for 'pneumonia and lower respiratory tract infection' when comparing elective CS with VD. Comparing emergency CS with VD this association was smaller for laryngitis and not significant for pneumonia and lower respiratory tract infection.

Another Danish registry study focused on hospitalization for RSV infection. Again the associated risk was higher for elective CS (27%) than for emergency CS (9%).

On the contrary, a Norwegian cohort study found no association between all CS or elective CS vs. VD for lower respiratory tract infections before the age of 36 months. Finally a large Australian registry study found an association for admissions for bronchiolitis after elective CS before the age of 12 months, but not in the second year of life. No association between elective caesarean delivery and pneumonia admissions was observed.

The causal nature of this association is difficult to prove with those observational studies, so there is low quality evidence that (elective) caesarean section is causal to increase the risk for the later development of respiratory infections from some studies, while other studies did not find associations.

**Main conclusion: in observational studies a potentially increased risk of respiratory infection is reported but there are many limitations to the evidence and results are conflicting across studies.**

#### 9.1.4 Atopy

##### 9.1.4.1 Background

In 2008, a meta-analysis including 26 studies concluded that delivery through CS was associated with a moderate risk increase for allergic rhinitis, asthma, hospitalization for asthma, food allergy/food atopy, but not with inhalant atopy or atopic dermatitis.<sup>84</sup> However, this meta-analysis did not consider the reason to choose for CS.

##### 9.1.4.2 Systematic reviews and meta-analyses

A review from 2015 assessed the association between mode of delivery and risk of atopy in childhood.<sup>85</sup> Because of a lack of transparency on the methods (search terms, inclusion and exclusion criteria) we discarded this review.

No other recent systematic reviews or meta-analyses have been identified.

Because no recent meta-analyses were identified we decided to use data from the older meta-analysis from Bager et al. (2008).<sup>84</sup> This gives only overall data for CS vs. VD and no more data on the reason to choose CS or whether it was elective or emergency CS. This meta-analysis included 26 primary studies: 10 on atopy, 8 on eczema or atopic dermatitis, 7 on allergic rhinitis and 20 on asthma hospitalizations. For each significant association with an allergic outcome, only 1 – 4% of cases were attributable to CS so the authors also concluded that the rise of the number of CS is an unlikely explanation for the observed 'allergy epidemic' (Table 3).



**Table 3 – Summary odds ratios in a random effects model for different outcomes (CS vs. VD)<sup>84</sup>**

Outcome	Nr studies	Summary OR (95% CI)
<b>Food allergy/food atopy</b>	6	1.45 (1.12 - 1.86)
<b>Inhalant atopy</b>	4	1.07 (0.82 - 1.38)
<b>Eczema/atopic dermatitis</b>	8	1.03 (0.98 - 1.09)
<b>Allergic rhinitis</b>	7	1.24 (1.08 - 1.43)

#### 9.1.4.3 Update with primary studies

No primary study published after the 2008 systematic review was retained (out of scope or very low quality level).

For the relation between atopy in the offspring in relation to caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

One meta-analysis from 2008 (of limited quality) is available. This study shows a potential association between increased risk for allergic rhinitis and food allergy for all CS vs VD. No information on the specific associated risk of elective CS vs. VD was found.

The causal nature of this association is difficult to prove with those observational studies, so there is very low quality evidence that (elective) caesarean section is causal to increase the risk for the later development of atopy.

**Main conclusion: there is potentially an increased risk for some atopy outcomes but evidence is poor.**

### 9.1.5 Diabetes mellitus type 1

#### 9.1.5.1 Background

A meta-analysis summarizing 20 studies from Cardwell et al. (2008) was identified.<sup>86</sup> This study showed that children born by CS have a 23% higher risk of developing childhood-onset type 1 diabetes compared to those vaginally born. This association was not altered by adjusting for confounders such as maternal age, birth order, birthweight, gestational age, maternal diabetes, or breastfeeding. However, this meta-analysis did not consider the reason of CS.

#### 9.1.5.2 Systematic reviews and meta-analyses

No SR published these last five years was found on this topic. So we present the data from the high-quality meta-analysis by Cardwell et al. (2008).<sup>86</sup>

In this well-documented meta-analysis twenty independent studies were identified with a search date up to September 2007. Of those studies 17 were case-control studies and three were cohort studies. For seventeen of those studies raw data were available for the analysis to enable additional correction for confounding. Measured confounders differed by study but included breastfeeding, birth order, birthweight, gestational age, maternal age and maternal diabetes. The total number of diabetes type 1 cases was 9 938.

Overall, there was a significant increase in the risk of diabetes type 1 in children born through CS compared to VD: adjusted OR was 1.19 (95% CI [1.04, 1.36]). The authors conclude that CS overall (elective and emergency) is associated with an approximately 20% risk increase for childhood-onset type 1 diabetes that cannot be explained by the measured confounders. Mean confounders that are associated with a higher risk of diabetes type 1 are: increasing birthweight, normal gestational age vs. gestational age >42 weeks, higher maternal age, higher birth order, maternal diabetes, no or short period of breastfeeding.



### 9.1.5.3 Update with primary studies

Of the 167 articles identified, four were retained.<sup>75, 78, 87, 88</sup> Moreover, the previously mentioned Danish study from Sevelsted et al. (2015) also looks at this outcome for all CS compared to VD.<sup>77</sup>

Several of the previously cited studies on asthma also dealt with other immune disorders that might be linked with CS vs VD.

1. The previously described study by Sevelsted et al. (see section 9.1.2. on asthma for more details on this study) also considered the outcome diabetes type 1 in the offspring.<sup>77</sup> In the crude analysis the risk for developing diabetes type 1 was higher with CS, but after adjustment, the results for type 1 diabetes was no longer statistically significant. This is mainly due to the fact that the proportion of CS in women with diabetes was much higher than in women without diabetes (27% vs. 14%). No relation was found after adjustment: the adjusted RR was 1.01 (95% CI [0.93, 1.10]) for all CS compared to VD.
2. A Swedish population-based cohort study using a sibling design<sup>87</sup> identified diabetes type 1 through the Swedish National Patient Registry and birth data through the Swedish Medical Birth Registry. Mode of delivery was categorized into unassisted VD (reference), instrumental VD (IVD), emergency and elective CS. This analysis was done on 2 638 083 singleton life births in Sweden between 1982 and 2009. At first a cohort analysis using a log-linear Poisson model was performed adjusted for several confounders: age, year of birth, gestational age, maternal (pre-pregnancy) diabetes, birth order and maternal age, BMI, country of birth education, gestational diabetes, and birth size compared to gestational age and preeclampsia. Some of these confounders were later removed from the model since they did not basically change the results. The second step was a sibling-control analysis using conditional logistic regression with the mother as the grouping variable to adjust for unmeasured familial environmental and genetic confounding factors shared by the siblings.

In the study, 79.4% were VD, 7.3% IVD, 6.1% elective CS and 7.1% emergency CS. The adjusted RR compared to VD was 1.15 (95% CI [1.06, 1.25]) for elective CS, 1.02 (95% CI [0.95, 1.11]) for emergency

CS and 1.14 (95% CI [1.06, 1.23]) for IVD. In the sibling analysis, 2 200 siblings discordant on mode of delivery and diabetes type 1 diagnosis were included. In this analysis the adjusted RR, in the sibling cohort adjusted analysis were 1.06, 1.6 and 1.07 for elective CS, emergency CS and IVD respectively, all of them not statistically significant.

The authors conclude that those findings are not consistent with a causal effect of mode of delivery on diabetes type 1 and that the association may be due to familial confounders such as genetic susceptibility and environmental factors.

3. A registry based retrospective cohort study from Black et al. (2015) in Scotland was described in more detail in section 9.1.2. on asthma.<sup>75</sup> This study also included the outcome diabetes type 1. In this study no significant differences in risk of type 1 diabetes between children born by VD and those born by planned CS delivery could be detected: adjusted RR 1.20 (95%CI [0.95, 1.52]) for the base analysis and 1.07 (95%CI [0.77, 1.50]) for the sensitivity analysis using only complete-cases.
4. A case-control study of Samuelsson et al. used a Swedish paediatric quality registry to investigate whether birth by CS is associated to the risk of developing diabetes type 1.<sup>88</sup> It includes children (age 0-18) diagnosed with the disease from 2000 to 2012 (n=9 376). Each of them was matched to four controls based on year, day of birth, sex and county of birth from the Swedish Medical Birth Registry.

Overall, 13.5% of deliveries were by CS. By group, 14.7% of children who developed type 1 diabetes were delivered by CS compared with 13.3% of control children ( $p < 0.001$ ). Mothers with diabetes more often gave birth by CS than mothers without diabetes (78.8% vs. 12.7%,  $p < 0.001$ ). In a logistic regression model adjusting for maternal age, maternal diabetes and BMI in early pregnancy, the OR for CS was 1.0. A child who developed type 1 diabetes and had a mother with type 1 diabetes at the time of delivery had the highest OR to have been born by CS. Children of mothers without diabetes, delivered by CS, had no increased risk of developing type 1 diabetes. Maternal diabetes was the strongest predictor of childhood diabetes (OR 3.4), especially if the mother had type 1 diabetes (OR 7.54). The authors conclude that CS



had no influence on the risk of type 1 diabetes during childhood or adolescence. However, maternal diabetes itself strongly increased the risk of offspring developing type 1 diabetes.

- Finally, the previously described Danish registry-based cohort study from Kristensen (see section 9.1.2. on asthma) also examined the outcome diabetes type 1.<sup>78</sup> This study showed no difference for diabetes in children from 0 to 14 years old when comparing elective or acute CS to VD. Adjusted HR were 0.93 and 1.05 for elective CS and acute CS respectively compared to VD (both not statistically significant).

For the relation between diabetes type 1 in the offspring in relation to caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

One meta-analysis from 2008 including twenty mainly case-control studies found that CS (both elective and emergency) was associated with a 20% risk increase for childhood diabetes type 1 compared with VD.

However, five large and more recent studies (four registry based and one case-control) found no such association. The Swedish study that also compared siblings with discordant mode of delivery or diabetes studies found an association in the crude analysis but not in the sibling analysis.

The causal nature of the association found in some studies is difficult to prove with those observational studies. As a result there is very low quality evidence from those conflicting results that (elective) caesarean section is causal to increase the risk for the later development of childhood diabetes type 1.

**Main conclusion: the previously reported increased risk of diabetes type 1 is not confirmed by recent analyses.**

## 9.1.6 Inflammatory bowel disease (IBD)

### 9.1.6.1 Background

The inflammatory bowel diseases are mainly composed by Crohn disease (CD) and ulcerative colitis (UC).<sup>89</sup> They have been considered to result from an inappropriate immune response where the intestinal commensal bacteria could play a role.<sup>77</sup> Because the intestinal colonization differs between children born by CS and VD, it has been hypothesised that mode of delivery can modify the risk of IBD.

### 9.1.6.2 Systematic reviews and meta-analyses

Two recent meta-analyses were found: Li et al. (2014) and Bruce et al. (2014).<sup>89, 90</sup> Both focused on the association of all types of CS and inflammatory bowel disease. While the study by Li et al. considered CD, UC and all IBD separately, the study by Bruce et al. considered IBD as one entity.

The meta-analysis by Li et al. (2014) includes nine studies: six dealt with CD, four considered UC and three investigated IBD as a whole.<sup>89</sup> All included studies used a case-control or a cohort design. For the meta-analysis, OR were calculated using a random effects model in the presence of important heterogeneity. For CD (six studies) the OR was 1.38 (95% CI [1.12, 1.70]) for 3 622 cases while for UC this was 1.07 (95% CI [0.87, 1.32]) for 1 404 cases. For IBD overall, the pooled random effects OR was 1.13 (95% CI [0.99, 1.30]) for 13 528 cases.

The review by Bruce et al. (2014) included seven studies, four retrospective cohort and three case-control studies.<sup>90</sup> The pooled odds ratio for all included studies in a random effects model for all IBD for CS delivery vs. VD was 1.00 (95% CI [0.75, 1.33]). However, separate analyses by study design showed some variation in the point estimate. However, none of them were statistically significant, except for the pooled estimate from case-control studies using questionnaires: OR 1.17 (95% CI [1.03, 1.32]). So this study observed no difference in risk of all IBD between both modes of delivery.

Although the meta-analysis by Li et al. (2014) specified the kind of inflammatory diseases (CD or UC) it did not specify the reason for CS.



However, three of the included studies considered elective CS separately.<sup>91-93</sup>

1. In the Danish national registry-based cohort (8 142 cases in children born 1973-2008), moderately but statistically significant increased rates of IBD in childhood, adolescence, and young adulthood (up to the age of 36 years) was observed after all kinds of CS vs VD: IRR 1.14 (95% CI [1.06, 1.22]).<sup>91</sup> This increase was more outspoken in the age span 0–14 years: IRR 1.29 (95% CI [1.11, 1.49]) but the difference with older cohort members was not statistically significant. However, even if the association were causal, the possible impact of increasing CS practices on the overall burden of IBD in childhood is likely to be small. Moreover, the effect of mode of delivery on IBD risk at age 0–14 years was higher for acute CS (IRR 1.51, 95% CI [1.01, 2.27]) than for elective CS (IRR 0.72, 95% CI [0.33, 1.53]), although this difference was not statistically significant.
2. The Swedish case-control study (1 536 cases with paediatric (i.e. < 16 years of age) CD born between 1973 and 2006) noticed a modestly increased paediatric CD risk for boys delivered by CS (OR 1.25, 95% CI [1.01, 1.54]) compared with VD but not in girls (OR 0.99, 95% CI [0.76-1.29]).<sup>92</sup> Elective procedures were associated with a raised paediatric CD risk in the entire population without difference according to the gender: OR 1.36 (95% CI [1.02, 1.80]).
3. A record linkage study utilizing perinatal records of children born in the state of Victoria, Australia between 1983 and 1998 looked at several early-life risk factors for the development of paediatric CD (diagnosis at < 16 years of age).<sup>93</sup> Further, a nested case control study was conducted to examine the association between sibling exposure and CD risk. The population included 1 005 054 live births and 278 cases of paediatric CD that could be record-linked. A nested case – control study within the main cohort was used to assess the relationship between risk of CD and the number of younger siblings and age difference between index children and younger siblings. For sibship structure, the exposure measures were birth order, total, older and younger sibling number, interbirth sibship intervals, cumulative exposure to younger infant

siblings prior to a specified index age range, and cumulative exposure to siblings prior to a specified index age range.

Among the early-life risk factors they found a higher risk of paediatric CD in children born by CS compared to spontaneous VD: adjusted HR are 1.67 for elective CS (95% CI [1.17, 2.39]), 1.50 for emergency CS (95% CI [0.99, 2.28]) and 1.95 for forceps or vacuum delivery (95% CI [1.45, 2.62]) all with spontaneous VD as a reference.

#### 9.1.6.3 Update with primary studies

The previously described study from Black in Scotland (see section 9.1.2. on asthma for more details on this study) concludes that there were no significant differences in risk of IBD between children born by VD and those born by planned CS delivery.<sup>75</sup> Adjusted HR was 0.86 (95% CI [0.50, 1.49]) and 1.30 (95% CI [0.62, 2.73]) in the complete-case analysis.

The previously described study from Kristensen et al. in a Danish cohort (see section 9.1.2. on asthma for more details on this study) found no association for the CD comparing elective or acute CS to VD and no association for the UC comparing elective CS to VD, and a just statistically significant association for acute CS (aHR 1.47 95% CI [1.02, 2.12]).<sup>78</sup>

Finally, the previously described Danish study from Sevelsted et al. (see section 9.1.2. on asthma for more details on this study) found an association between all cause CS vs. VD: aIRR 1.20 (95% CI [1.06, 1.36]).<sup>77</sup>



For the relation between inflammatory bowel disease (IBD) in the offspring in relation to caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

Two recent meta-analyses analysed the effect of CS (for all reasons). One of those made the distinction between Crohn disease (CD), ulcerative colitis (UC) and IBD. The other considered IBD as one entity. In the meta-analysis considering the different forms of IBD the association was statistically significant for CD only while it was not significant for UC. Also the overall effect on IBD was not significant. For the other meta-analysis, most of the results were not statistically significant except for one subgroup of studies based on questionnaires.

Three of the studies included in the first analyses also looked specifically at the effects of elective CS: these show mixed results.

The causal nature of the association found in some of these studies is difficult to prove with those observational studies. As a result there is very low quality evidence from those conflicting results that (elective) caesarean section is causal to increase the risk for the later development of childhood inflammatory bowel disease.

**Main conclusion: the association between (elective) CS and IBD provides conflicting results.**

## 9.1.7 Gastro-enteritis

### 9.1.7.1 Background

According to some authors, colonization patterns play important roles in tolerance induction, mucosa-associated barrier defences against pathogens, and in the development and homeostasis of innate and adaptive immunity to pathogens. Increasing CS practices may therefore impact on susceptibility to infections with intestinal bacteria.<sup>94</sup>

### 9.1.7.2 Systematic review and meta-analysis

No recent systematic review or meta-analysis was found on this topic.

### 9.1.7.3 Update with primary studies

The Danish cohort from Bager et al. focused specifically on intestinal bacterial infection. In a cohort of 1.7 million Danes born between 1973 and 2005<sup>94</sup> they identified cases of laboratory-confirmed non-typhoid species through national registries. Confounder-adjusted IRRs for infections according to mode of delivery were calculated. However, this study did not distinguish between emergency or acute CS, nor for the reason of CS (medical or non-medical). This study showed that during 14 million person-years of follow-up, 22 486 individuals were diagnosed with one intestinal bacterial infection. CS was associated with a small increase in risk at age 1 to < 2 years (IRR, 1.09; 95% CI [1.00, 1.18]) and at age 2 to < 5 years of age (IRR, 1.08; 95% CI [1.00, 1.17]), but before the age of 1 and from age 5 years, there was no statistically significant association. The authors conclude that individuals delivered by CS were at an overall 5% (overall adjusted IRR 1.05, 95% CI [1.01, 1.09]) increased risk of intestinal bacterial infections compared with vaginally delivered peers, a finding that was essentially restricted to infections in children > 1 and < 5 years of age (after age 5 years, there was no significant association).<sup>94</sup> Mode of delivery appears thus not to be a clinically relevant determinant of risk for intestinal bacterial infections. The possible impact of increasing frequencies of CS on the overall burden of intestinal bacterial infections appears negligible.

The previously described Danish cohort from Kristensen et al. based on hospital registries (see section 9.1.2. on asthma for more details on this study) found an association comparing elective or acute CS to VD for the risk of gastro-enteritis between 0-14 years.<sup>78</sup> Adjusted hazard ratios were 1.18; 95% CI [1.13, 1.23] for elective CS and 1.22; 95% CI [1.17, 1.27] for acute CS without a statistically significant difference between both modes of CS delivery.



For the relation between inflammatory gastroenteritis in the offspring in relation to caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

No meta-analyses or systematic reviews were found.

Two large Danish studies were found: one based on laboratory diagnosis registries, the other on hospital diagnosis records. The study on laboratory confirmed cases shows a small (5% effect overall, statistically significant) of all CS vs. VD but basically only in children between 1 and <5 years. The other study based on hospital diagnoses showed a statistically significant effect in ages 0-14 of around 18% but without an important difference between elective and acute CS.

The causal nature of the association found in some of these studies is difficult to prove with those observational studies. As a result there is very low quality evidence from those conflicting results that (elective) caesarean section is causal to increase the risk for the later development of childhood gastro-enteritis.

**Main conclusion: there is an apparent association between CS (both elective and emergency) and gastro-enteritis but with conflicting results at different ages depending on the origin of the diagnosis. However, this possible association seems to have a negligible effect on the overall burden of disease.**

## 9.1.8 Coeliac disease

### 9.1.8.1 Background

The assumption that the bacterial flora of the newborn may play a role in the development of coeliac disease was often quoted in the literature. A retrospectively case-control study from Decker et al. reported an increased risk of coeliac disease after CS.<sup>95</sup> However, this study considered all kind of CS and had a low power (157 individuals with coeliac disease) and a lack of data on potential confounders.

### 9.1.8.2 Systematic reviews and meta-analyses

No recent SR was found on this topic.

### 9.1.8.3 Update with primary studies

The previously described Danish study from Sevelsted et al. (see section 9.1.2. on asthma for more details on this study) also looked at coeliac disease.<sup>77</sup> They found no association between all cause CS vs. VD: aIRR 0.98 (95% CI [0.87, 1.14]).

The Swedish study from Mårild et al. is a population-based case-control study examining the risk of coeliac disease in individuals exposed to CS.<sup>96</sup> Prospectively recorded pregnancy data were obtained from the Swedish Medical Birth Registry between 1973 and 2008. Study participants consisted of 11 749 offspring with biopsy-verified coeliac disease identified through histopathology reports from Sweden's 28 pathology departments and 53 887 age- and gender matched controls from the general population. This study found a positive association with elective, but not with emergency CS and later coeliac disease (average age at diagnosis = 7 years). The adjusted OR for elective CS was 1.15 (95% CI [1.04, 1.26]). For emergency CS this adjusted OR was a non-statistically significant 1.02.

The Norwegian registry-based retrospective case-control study from Emilsson et al. contains pregnancy information on 95 200 women and data on their 114 500 children collected between 1999 and 2008.<sup>97</sup> It is linked to the Nation Birth Registry and the National Patient Registry and also uses women's responses to questionnaires. It identified 650 children with coeliac disease and 107 828 controls. It did not find an association between modes of delivery with coeliac disease in children (before age 7 years). Two models for adjusting were used but none showed statistically significant results. Adjusted OR were for CS (elective or not) vs. VD 0.84 and 0.83 for model 1 and model 2 respectively. None of these adjusted OR were significant.<sup>97</sup>

Similarly, the previously described Danish cohort from Kristensen et al. but based on hospital registries (see section 9.1.2. on asthma for more details on this study) found no association comparing elective CD to VD for the risk of coeliac disease.<sup>78</sup> However this study mentioned a possible association with acute CS. For elective CS, the adjusted hazard ratio was a non-



significant 0.69 compared to VD and for acute CS it was 1.52 (95% CI [1.06; 2.20]).

For the relation between coeliac disease in the offspring in relation to caesarean section vs. vaginal delivery only observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

No meta-analyses or systematic reviews were found.

Four individual studies with Scandinavian cohorts were found: all based on registry data. Data are conflicting: a Danish registry study compared all CS vs. VD and no association was found after adjusting for confounders. In a Swedish study using histopathology reports there was a statistically significant association for elective CS and none for emergency CS, both compared to VD. In a Norwegian study (not differentiating between elective or emergency CS) no association was found. In another Danish registry study the results were significant for emergency (acute) CS, but not for elective CS. So results are very conflicting, also considering the role of elective vs. emergency CS.

The causal nature of the association found in some of these studies is difficult to prove with those observational studies. As a result there is very low quality evidence from those conflicting results that (elective) caesarean section is causal to increase the risk for the later development of coeliac disease.

**Main conclusion: the results for the association between (elective) CS and coeliac disease are very conflicting and no real conclusion can be drawn from those results.**

## 9.2 BMI, overweight, obesity

### 9.2.1 Background

Caesarean section delivery has been suspected to have an influence on development and functions of both innate and acquired immunity, and following risk of disease.<sup>72</sup> Consequently, the association between CS and immune diseases was explored in large cohort studies. A relation between CS and later-life obesity has also been postulated because both CS rates and obesity prevalence in children and adults are steadily increasing worldwide. The hypothesized biological mechanism by which delivery mode is associated with children weight status is through its impact on the intestinal microbiome of the child.<sup>98</sup> The gut flora of infants born by vaginal delivery is similar to the maternal vaginal microbiota while the gut flora of infants delivered by caesarean section is colonized later and less frequently by *Bacteroides* species and *Bifidobacterium* species, that are often lacking in obese persons.

These last years, a lot of epidemiological studies (case-control, retrospective or prospective cohort studies) were conducted in order to check the association between the delivery mode and the subsequent overweight or obesity measured during the childhood or the adulthood. Unfortunately, most of the studies failed to consider important potential confounders, including parental obesity, morbidity during pregnancy (e.g. gestational diabetes), breastfeeding or socioeconomic status. Moreover, these studies have been small sized and led to contradictory results.

### 9.2.2 Systematic reviews and meta-analyses

Three recent systematic reviews tried to evaluate whether an association exists between caesarean section and overweight/obesity in offspring but also in adults and to determine the strength of the association.

#### 9.2.2.1 Childhood obesity

A recent systematic review was published in 2015 (Kuhle et al. 2015, and searched for studies published up to July 2014).<sup>98</sup> The quality of the SR was moderate (Amstar 7/11). It investigated the association between the mode of delivery and the overweight or obesity in children (2-18 years). A total of



24 publications reporting 28 studies were included in the analysis. They were conducted in 15 countries or regions, with Brazil (n = 5), the United States (n = 5) and China (n = 3) contributing nearly half of the studies. The median age at BMI assessment was 6 years (range 2–15 years). Caesarean section had a pooled RR of 1.34 (95% CI [1.18, 1.51]) for obesity in the child compared with VD (n = 19 studies). When overweight was the outcome of interest, the pooled RR was 1.16 (95% CI [1.06, 1.27]) for CS compared with VD (n = 13 studies). Adjustment for maternal pre-pregnancy weight did not change this association. The pooled effect decreased by 18% but the RR remained statistically significant after adjustment. No study included in this review adjusted for gestational diabetes. Results showed that all CS increased the risk of developing obesity in childhood (34% increase) and this is validated by the study considering the indication of CS (1 Chinese cohort study).

#### 9.2.2.2 *Childhood and adulthood obesity*

In 2013, Li et al. published a systematic review and meta-analysis including 7 cohort and 2 case-control studies that reported the association of caesarean section with childhood (3–8 years), adolescence (9–18 years) and/or adult (>19 years) overweight/obesity.<sup>99</sup> The overall pooled odds ratio (OR) of overweight/obesity for offspring delivered by CS compared with those born vaginally was 1.33 (95% CI [1.19, 1.48];  $I^2=63%$ ); the OR was 1.32 (95% CI [1.15, 1.51]) for children, 1.24 (95% CI [1.00, 1.54]) for adolescents and 1.50 (95% CI [1.02, 2.20]) for adults. In subgroup analysis, the overall pooled OR was 1.18 (95% CI [1.09, 1.27];  $I^2=29%$ ) for high-quality studies. Such results showed that caesarean section was moderately associated with offspring overweight and obesity. Unfortunately, the reason for performing CS was not specified, and the meta-analysis did not conduct subgroup analysis by type of CS.

Later, Darmasseelane et al. conducted a high quality systematic review (AMSTAR 10/11) and meta-analysis of the effect of Caesarean section (CS) and vaginal delivery (VD) on offspring BMI, overweight (BMI>25) and obesity (BMI>30) in adulthood ( $\geq 18$  years).<sup>100</sup> Secondary outcomes were subgroup analyses by gender and type of CS (in-labour/emergency, pre-labour/elective). Type of exposure was classed as VD (including natural, forceps and vacuum extraction) and CS, with CS groups further categorised

as Pre-Labour CS or In-Labour CS). In total, 15 studies were included (combined population n=163 753); among them only 4 compared elective caesarean section to VD (n= 17 923 women; pre-labour-CS = 261, VD = 17 662).

The following results were ported:

- **BMI:** whereas the mean BMI difference was significant in pooled-gender unadjusted analyses comparing all CS to VD (0.44 kg/m<sup>2</sup>; 95% CI [0.17, 0.72]; p=0.002), such difference was not more significant in subgroup analysis comparing elective/pre-labour-CS to VD (mean BMI difference: 0.32 kg/m<sup>2</sup>; 95% CI [0.21, 0.85]; p=0.24). Heterogeneity was low in all primary analyses. Similar results were found in gender-specific subgroup analyses. Subgroup analyses comparing types of CS to VD showed no significant impact on any outcome.
- **Overweight:**
  - OR for incidence of overweight: 1.26 (95% CI [1.16, 1.38]; p<0.00001), comparing all CS to VD in pooled-gender unadjusted analyses.
  - OR for incidence of overweight: 1.20 (95% CI [0.93, 1.55]; p=0.15) in subgroup analysis (4 studies) comparing elective/pre-labour-CS to VD.
- **Obesity:**
  - OR for incidence of obesity: 1.22 (95% CI [1.05, 1.42]; p=0.01), comparing all CS to VD in pooled-gender unadjusted analyses.
  - OR for incidence of obesity: 1.13 (95% CI [0.80, 1.59]; p=0.50) in subgroup analysis (3 studies) comparing elective/pre-labour-CS to VD.

Globally, a strong association between CS and increased offspring BMI, overweight and obesity in adulthood is shown in this meta-analysis. This association is not more confirmed in subgroup analysis for elective CS. However, the number of pre-labour CS delivered participants included in the subgroup analyses was <10% of the total number of CS deliveries in the main meta-analysis. The results need to be interpreted with caution due to



the absence of clear identification of the CS reason (medical or not), the lack of power for the subgroup analyses, the lack of data related to the main confounding variables in most of the included studies (e.g. maternal BMI, gestational diabetes and socioeconomic status). A lack of patient level data hampered adjustment for confounders.

### 9.2.3 Update with primary studies

#### 9.2.3.1 Childhood obesity

Mueller et al. (2015) investigated two hypotheses that CS and antibiotic use during the second or third trimester of pregnancy are independently associated with higher childhood obesity risk and levels of adiposity after controlling for important confounders, including maternal pre-gravid BMI, birth weight and breastfeeding in the first year of life.<sup>101</sup> Data came from participants in the Columbia Center for Children's Environmental Health Mothers and Newborns Study in Northern Manhattan and the South Bronx in New York (a longitudinal birth cohort study (1998-2006) aimed to evaluate the effects of prenatal exposures to ambient and indoor pollutants on birth outcomes, neurocognitive development, and procarcinogenic damage among a cohort of mothers and newborns from minority communities in New York City). From 727 mother-child dyads enrolled, 611 were analysed. Of these, 436 children (71.4%) at 7 years of age were followed-up with measured BMI (VD: n=337; CS: n=99). At 7-year of follow-up, the association was significantly different for elective CS (RR 1.53; 95% CI [1.04, 2.25]) compared with VDs. This relative risk was adjusted for sex, ethnicity, offspring birth weight, maternal age, maternal pre-gravid BMI, receipt of public assistance during pregnancy, prenatal antibiotic use or delivery mode, having breastfed in first year and after exclusion of mothers diagnosed with gestational diabetes and preeclampsia during pregnancy (N=411). Authors concluded that independent of prenatal antibiotic usage and other confounders, CS was associated with 46% (8-98%) higher risk of childhood obesity at 7 years than vaginally delivered children.

The second study is a population-based retrospective cohort study conducted in Scotland (1993-2007) aiming to examine the relationship between planned caesarean delivery and offspring health problems or death in childhood.<sup>75</sup> The following outcomes were explored: asthma, obesity,

inflammatory bowel disease, type 1 diabetes, cancer, and death. The study sample included data on 321 287 term first-born singletons followed until February 2015. The study was considered as having low risk of bias. Obesity at age 5 years (11.26% vs 9.39%; difference, 1.87% (95% CI [1.34%, 2.39%]; adjusted HR, 1.12 (95% CI [0.99 to 1.26]) appeared more likely following planned caesarean delivery compared with vaginal birth in univariate analysis, but this was not significant after adjustment. The HR was adjusted for maternal age, maternal body mass index, gestation at birth, maternal Carstairs decile (represents an ordinal measure from 1 (most affluent) to 10 (most deprived), used as a surrogate for social class), maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks. Authors concluded that there were no significant differences in risk of obesity at 5 years between children born by VD and those born by planned CS delivery.

#### 9.2.3.2 Adulthood obesity

Mamun et al. (2013) examined the association between the mode of delivery and the risk of offspring obesity by age **21 years** using a large community-based birth cohort study in Australia (n = 2625 young adults followed-up).<sup>102</sup> Of them, 12.1% were delivered by CS. Two measures were used to define overweight and obesity. Mothers who were heavy smokers during pregnancy, had hypertensive disorder of pregnancy, delivered after 35 years of age, had premature birth, delivered a low-birth-weight newborn, and were overweight or obese before pregnancy had a greater risk of caesarean delivery. Firstly, using BMI measures (overweight  $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$ ; obesity  $\text{BMI} \geq 30 \text{ kg/m}^2$ ). Secondly, using waist circumference, measured horizontally using a tape approximately in line with the umbilicus, directly against but without compressing the skin. The average of two measures was taken. Waist circumference was categorized for males as follows: less than 94 cm was normal; 94 to less than 102 cm was overweight; and 102 cm or more was obese; and for females it was categorized as follows: less than 80 cm was normal; 80 to less than 88 cm was overweight, and 88 cm or more was obese. Using BMI cut-offs, 21.5% of young adults were overweight and 12.4% were obese. In the same way, using the waist circumference cut-off, 14.2% of young adults were overweight and 13.5% were obese. In the unadjusted and adjusted models, odds of being overweight and obese at



age 21 years were not significantly different for babies delivered by caesarean and those delivered vaginally. Differentiating between elective and emergency caesarean had little impact on the observed associations. The main strength of this study was a prospective follow-up of a large cohort of mothers and offspring dyads. Potential confounders and mediators including parental pre-pregnancy BMI, gestation, low birth weight, and duration of breastfeeding were considered in the analyses. Authors concluded that mode of delivery is not associated with long-term BMI, waist circumference scores, or obesity. The mode of delivery (or caesarean) appears to be a confounder, rather than a causal factor, in the development of overweight and obesity in (young) adulthood of offspring.

The more recent systematic reviews and meta-analyses showed positive relationships between all kinds of caesarean deliveries and increased offspring BMI, overweight and obesity in adulthood.<sup>99, 100</sup> For the highest quality SR<sup>100</sup> this association was not confirmed in subgroup analysis for elective CS (representing <10% of the total number of CS deliveries in the main meta-analysis). A lack of individual patient data hampered adjustment for confounders.

Large primary studies published later reported inconsistent results: a large longitudinal study among a cohort of mothers and newborns from minority communities in New York City<sup>101</sup> reported a positive association between CS and obesity at 7 years whereas a population-based retrospective cohort study conducted in Scotland<sup>75</sup> concluded that there were no significant differences in risk of obesity at 5 years between children born by VD and those born by planned CS delivery. Finally, a large prospective cohort study conducted in Australia reported that the risks of being overweight and obese at age 21 years were not significantly different for babies delivered by caesarean and those delivered vaginally.<sup>102</sup> Differentiating between elective and emergency caesarean had little impact on the observed associations.

Childhood overweight and obesity is a multifaceted health issue. The main reasons of excess weight in childhood and adolescence are similar to those in adults, including individual causes such as behaviours, underlying disorders and genetics.

Behaviours can include dietary patterns, level and frequency of physical activity, medication use, and other exposures. Additional contributing factors include the food and physical activity environment, education and skills, and food marketing and promotion (CDC, 2015; see <http://www.cdc.gov/obesity/childhood/causes.html>).

None of these main factors were investigated in epidemiological studies that explored the association between delivery mode and increased BMI in later-life.

**Main conclusion: The mode of delivery could act like a confounder, rather than a causal factor, in the development of overweight and obesity in (young) adulthood of offspring.**

## 9.3 Childhood cancer

### 9.3.1 Background

Caesarean section delivery has been called into question about its impact on development and functions of both innate and acquired immunity, and following risk of disease.<sup>72</sup> This is the reason why many researchers have investigated the association between caesarean delivery and immune diseases. In the same vein, scientists are interested to explore the relation between caesarean delivery and subsequent cancer risk.

Three potential mechanisms have been reported, by which the mode of delivery may disturb the immune system, and subsequent cancer risk.<sup>103</sup> First, the microbiome of the newborn is impacted by the mode of delivery: children born by a caesarean section were not exposed to maternal vaginal and intestinal microbiota and compared to children delivered vaginally, suffered of a lack of Bifidobacterium species; their gut flora may be altered for months or even years after birth. Second, due to the absence of labour in planned CS, no stress response initiates the cortisol release and hypothalamic–pituitary–adrenal axis activation useful for the gut and immune system maturation. Third, differences in the epigenetic regulation of genetic expression have been suggested to be a factor; leucocytes in cord blood of offspring delivered by planned CS demonstrate higher levels of



DNA methylation. These diverse playing mechanisms mean that the risks for childhood cancers may differ by type of CS.<sup>103</sup>

### 9.3.2 Systematic reviews and meta-analyses

No recent SR was found on this topic

### 9.3.3 Update with primary studies

Three primary studies found owing the update of systematic reviews investigating the relationship between delivery mode and immune disorder were retrieved and their quality was critically appraised.

A large cohort study of moderate quality was conducted in three Nordic countries (Denmark, Sweden and Finland) to investigate the association between delivery by caesarean section and risk of childhood cancer.<sup>103</sup> It examined the risk of childhood cancer in general, and the risks of specific childhood cancers. This study was partly financed by the European Research Council and the European Commission's Seventh Framework Programme (FP7)]. This cohort study used nationwide data from Denmark, Finland and Sweden between 1973 and 2007 and covered a population of 7 029 843 children. The follow-up started at birth, and ended at the first of the following events: relevant cancer diagnosis, death, emigration, the day before the 15<sup>th</sup> birthday or end of follow-up (31 December 2006 in Sweden, 31 December 2007 in Denmark and 31 December 2010 in Finland). The total follow-up time was 79 571 514 person years. Children diagnosed with cancer within 6 months of birth and children who did not have a date of cancer diagnosis were excluded. Caesarean section was the mode of delivery for 882 907 children (12.6%); of these, at least 30.3% were delivered by an elective CS (n = 267 603). In the cohort, 11 181 children were diagnosed with cancer (incidence rate of 13.77 per 100 000 person years), the most common being leukaemia (n = 3 559), cancers of the central and sympathetic nervous systems (n = 2 779), renal tumours (n = 726) and non-Hodgkin's lymphoma (n = 636). This study concluded that there was no evidence of an increased risk of childhood cancer for children born by caesarean section (Hazard ratio 1.05; 95% CI [0.99, 1.11]). No substantial differences were obtained when stratifying results by type of CS.

The second study<sup>75</sup> is a population-based retrospective cohort study conducted in Scotland (1993–2007) aiming to examine the relationship between planned caesarean delivery and offspring health problems or death in childhood. The following outcomes were explored: asthma, obesity, inflammatory bowel disease, type 1 diabetes, cancer, and death. The study sample included data on 321 287 term first-born singletons followed until February 2015. The study was considered as having low risk of bias. There was no significant difference in risk of cancer (0.23% vs. 0.21%; difference 0.02%, 95% CI [–0.01%, 0.05%]; adjusted HR, 1.05, 95% CI [0.72, 1.55]) following planned caesarean delivery compared with vaginal birth. The HR was adjusted for maternal age, gestation at birth, maternal Carstairs decile (represents an ordinal measure from 1 (most affluent) to 10 (most deprived), used as a surrogate for social class), maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks. Authors concluded that there were no significant differences in risk of cancer between children born by VD and those born by planned CS delivery.

The third study is a population- and registry-based cohort study based on all children born in Denmark from January 1997 through December 2012.<sup>78</sup> It aim was to explore the associations between acute versus elective CS and disease associated with immune function in the offspring. The following outcomes were evaluated: asthma, laryngitis, gastroenteritis, ulcerative colitis, Crohn and coeliac disease, respiratory tract infection, juvenile idiopathic arthritis and cancer (lymphatic leukaemia, myeloid leukaemia, malignant lymphoma, and non-haematologic cancer (ICD-10 codes C00.0–C80.9)). Among the 1 031 424 children born during the period, 790 569 children aged 0 to 14 years were included in the study sample. Of these, 63 811 (8.1%) were born by elective CS, and 60 319 (7.6%) were born by acute CS. Children were followed from the day of birth to an outcome of diagnosis, emigration, death, or the end of follow-up on December 31, 2012. Hazard ratios for diseases associated with immune function in children delivered by acute and elective CS with vaginal delivery as the reference were calculated by using Cox regression. All analyses were adjusted for gestational age, sex, birth weight, maternal age, maternal smoking during pregnancy, and complications during pregnancy (preeclampsia, eclampsia, haemorrhage, and hyperemesis).

**Table 4 – Hazard ratios for cancers in children delivered by CS**

Type of cancer	Adjusted HR for elective CS (95% CI)	Adjusted HR for acute CS (95% CI)	p-value
Lymphatic leukaemia (ICD-10 codes C91.0-9)	1.03 (0.62-1.70)	1.20 (0.78-1.85)	0.34
Myeloid leukaemia (ICD-10 codes C92.0-9)	0.92 (0.32-2.66)	1.57 (0.67-3.67)	0.47
Malignant lymphoma (ICD-10 codes C81.0-85.9)	0.62 (0.19-2.06)	0.84 (0.30-2.32)	0.65
Non-haematologic cancer (ICD-10 codes C00.0-80.9)	0.92 (0.62-1.36)	0.78 (0.53-1.17)	0.85

This study, discriminating between acute and elective CS, could not confirm a hypothetical effect of CS on the risk of childhood leukaemia, lymphoma or non-haematologic cancer.

Caesarean section rates are increasing in most European countries, and even a very small rise in childhood cancer risk resulting from CS would have public health impact.<sup>75</sup> However, the results from three large, population-based studies across 4 European countries (Scotland, Denmark, Sweden and Finland) suggest no association between delivery by CS and childhood cancer in general, and for the most common types of childhood cancer (including leukaemia, cancers of the central and sympathetic nervous systems, renal tumours and non-Hodgkin's lymphoma). For less common types of childhood cancer, the numbers of cases were too small to provide any strong conclusions.

**Main conclusion: It seems unlikely that delivery by CS is an important contributor to individual risk of childhood cancer, despite the reported associations between CS and specific immune diseases.**

## 9.4 Developmental and behavioural outcomes

### 9.4.1 Background

Birth by CS has been linked to psychological development through adulthood in animal models. Some studies have linked birth by CS to an increased risk of autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and other behavioural difficulties but results are inconsistent.<sup>104</sup>

One of the reasons for this inconsistency is the difficulty to objectively measure this outcome and the different tools that are used. Another problem is that the age of the children at which this is assessed differs highly between studies making results difficult to compare.



### 9.4.2 Systematic reviews and meta-analyses

No systematic reviews were identified.

### 9.4.3 Update with primary studies

A recent study by Curran et al. (2016) assesses this association between CS vs. VD and the psychological development at age 7 years.<sup>104</sup> This study was done within British Millennium cohort of children study including 13 141 children born between 2000 and 2002. Only singleton births were included.

Information was gathered through five parental surveys at 9 months, 3, 5, 7 and 11 years. At nine months information was obtained from mode of delivery and potential confounders. This study assesses different modes of delivery (planned CS, induced CS, emergency CS, spontaneous VD, induced VD and instrumental VD).

At 5 and 7 years respondents were asked whether a doctor or health professional had ever told them that their child had ADHD or ASD. Behavioural difficulty was only assessed at age 7 using the Strengths and Difficulties Questionnaire (SDQ). The SDQ measures behavioural difficulties in five areas: conduct problems, hyperactivity, emotional symptoms, peer problems and pro-social behaviours. All scores except pro-social can be combined to create a “total difficulties” score.

Compared to spontaneous VD no associations were found between any mode of delivery and ADHD or ASD. For example, for planned CS the aOR for ASD was 0.58 (95% CI [0.19, 1.79]) and for ADHD it was 0.54 (95% CI [0.18, 1.64]).

For all behavioural difficulties assessed by SDQ there was only a borderline significant association between induced VD vs. spontaneous VD in the unadjusted analysis (OR 1.26; (95% CI [1.03, 1.54])), but not in the adjusted analysis OR 1.15 (95% CI [0.82, 1.60]).

Another study by Al Khalaf et al. (2015) includes children born between December 2007 and May 2008 (n = 11 134).<sup>105</sup> Children were selected randomly and recruited in the Growing Up in Ireland study. Data were weighted to represent the national sample (n = 73 662). Children where the

primary caregiver was not the mother were excluded (n=38) because most of the potential confounders are related to the mother.

Parental questionnaires were completed by trained interviewers through face-to-face interviews. This data collection was done at 9 months and 3 years. Response rate at the first wave of interviews was 65%. From these, 91% participated to the second wave.

At the first interview the mode of delivery and several confounders were assessed. Mode of delivery was categorized in SVD, IVD, elective CS and emergency CS. At this moment the Ages and Stages Questionnaire (ASQ) was used to assess the behavioural, cognitive and motor developmental outcomes. At age around 3 years the SDQ was used (see study by Curran et al. above). Results are reported as adjusted OR (aOR) with SVD as the reference.

At age 9 months, elective CS was associated with a delay in personal social skills (aOR 1.24; (95 % CI [1.04, 1.48]) and gross motor function (aOR 1.62, (95 % CI [1.34, 1.96]), whereas emergency CS was associated with delayed gross motor function (aOR 1.30, (95 % CI [1.06, 1.59]).

At age 3 years there was no significantly increased risk of an abnormal total SDQ score across all modes of delivery.

The authors concluded that children born by elective CS may face a delay in cognitive and motor development at age 9 months, but no increase in total SDQ score was found across all modes of delivery at age 3.

However, so many comparisons have been made in this study that some statistically significant results could be chance findings. Moreover, the relevance of these findings at 9 months is unclear.

Finally, a small case-control study by Kelmanson et al. (2013) was excluded because it was of very low quality.<sup>106</sup>



For the relation between developmental and behavioural outcomes in the offspring in relation to caesarean section vs. vaginal delivery only limited observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

No meta-analyses or systematic reviews were identified.

Two large cohort studies were included. Both studies used parental questionnaires to assess baseline although one study used trained interviewers. In both studies baseline information on mode of delivery and potential confounders was gathered.

At 7 years no association between mode of delivery and attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorders (ASD) could be detected in one study. Also for the outcome 'behavioural difficulties' assessed by SDQ no statistically significant association was found.

The other study assessing the children at 9 months found a few statistically significant associations with an increased risk with the ASQ instrument. They conclude that children born through elective caesarean section might have some delay in cognitive and motor function, while children born through emergency CS may have some delay in motor function. However, due to the many comparisons in this study this might be chance findings or confounding by indication (reason to perform a CS). At age 3 this study finds no association between mode of delivery and total SDQ score.

**Main conclusion: there is no evidence for an association of mode of delivery and ADHD, ASD or behavioural difficulties.**

## 9.5 Long-term child mortality

Black et al. (2015) conducted a population-based retrospective cohort study in Scotland (1993–2007) aiming to examine the relationship between planned CS delivery and offspring health problems or death in childhood.<sup>75</sup> Different outcomes were explored including death by age 21 years. The study sample included data on 321 287 term first-born singletons followed until February 2015.

The study concluded that in comparison with children born through VD, offspring born by planned CS, were at increased risk of all cause death by the age of 21, 0.40% vs. 0.32% with a difference of 0.08% (95% CI [0.02% to 1.00%]). The adjusted HR was 1.41 (95% CI [1.05, 1.90]). The study was considered as having a low risk of bias. The HR was adjusted for maternal age, gestation at birth, maternal Carstairs decile (represents an ordinal measure from 1 (most affluent) to 10 (most deprived), used as a surrogate for social class), maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks. However, important confounders such as maternal education, ethnicity, and in particular indication for caesarean delivery may confound the relationships studied.

For the relation between long-term child mortality in relation to caesarean section vs. vaginal delivery only limited observational evidence is available and experimental evidence (randomized clinical trials) is non-existent.

No meta-analyses or systematic reviews were identified.

One population-based retrospective cohort study tested the association between mode of delivery and offspring all cause death by age 21 years. A risk difference of 0.08% was found but the indication of CS, susceptible to confound the relationship, was not reported.

**Main conclusion: there is no evidence for an association of mode of delivery and long-term child mortality.**



## 10 IMPACT ON FUTURE PREGNANCIES: OFFSPRING OUTCOMES

### 10.1 Stillbirth in subsequent pregnancies

#### 10.1.1 Background

Stillbirth is not so easy to define since no one classification system is universally accepted, with varying descriptions of stillbirth used by researchers, countries, health organisations, and classification schemes. Stillbirths can be defined according to gestational age at birth typically into early stillbirths (20–28 weeks gestation) and late stillbirths (>28 weeks) or according to foetus weight (e.g. any foetus born weighing more than 400 grams in Australia).<sup>107</sup> Additionally stillbirths are classified into antepartum (death occurring before the onset of labour) or intrapartum (death during or after labour). Moreover, many systems include both stillbirths and neonatal deaths.<sup>107</sup>

Main causes or risk factors of stillbirth are well-known and are widely common. They include non-exhaustively placental insufficiency with fetal growth restriction, infection, pre-eclampsia, congenital abnormalities, placental abruption and umbilical cord accidents, advanced maternal age, high BMI, maternal conditions such as pre-eclampsia, diabetes and hypertension.<sup>107</sup>

#### 10.1.2 Systematic reviews and meta-analyses

O'Neill (2013) did a systematic review (search date November 2011) and meta-analysis to compare the risk of stillbirth in a subsequent pregnancy in women with a previous CS or VD.<sup>107</sup> Eleven studies were included in the stillbirth review, nine cohort studies and two cross-sectional studies totalling 1 961 829 pregnancies and 7 308 events (0.37%). A random-effects model is used due to considerable heterogeneity between the studies in the fixed-effect model ( $I^2 = 84.2\%$ ,  $p > 0.00001$ ). The pooled adjusted OR of stillbirth among women with previous CS versus VD was 1.23 (95% CI [1.08, 1.40]). Subgroup analysis by cause of stillbirth gave an OR of 1.47 (95% CI [1.20, 1.80]) for studies including unexplained stillbirths, an OR of 2.11 (95% CI

[1.16, 3.84]) for the single study which reported an estimate for explained stillbirths and an OR of 1.27 (95% CI [0.95, 1.70]) for antepartum stillbirths.

The overall findings of the meta-analysis suggest that women who had a previous CS have a 23% increased risk of subsequent stillbirth compared to women who have previously delivered vaginally. The significant effect of CS on stillbirth was present in the overall meta-analysis and persisted in the subgroup analyses by cause of stillbirth (explained, unexplained). Most studies in the meta-analysis adjusted for the following potential confounders: maternal age, smoking, history of pregnancy loss, gestational age and parity. On the other hand, adjustment for other potential confounders including BMI, socioeconomic status, marital status, maternal height, birth weight, medical complications such as diabetes or hypertension and race/ethnicity varied between the studies. The main confounder or source of selection bias is probably the indication for CS, and this is difficult to adjust for in a credible way. Heterogeneity in this meta-analysis is high and can be explained by variations in the definition of stillbirth used, cause and timing of stillbirth and by study design and parity. The Cochrane collaboration does not recommend the meta-analysis of such heterogeneous observational studies.

#### 10.1.3 Update with primary studies

O'Neill et al. (2014) reported the result of a population-based cohort study, using nationwide registry data.<sup>56</sup> This study covered the period from 1982 to 2010 in Denmark. Index live births included singleton and multiple gestation (twins or more) deliveries. In this study, women were followed up from the date of birth of the first child until the subsequent reproductive event of interest or until censoring due to live birth, death, emigration, or study end (December 31, 2010). Stillbirth was defined as the death of a foetus at 28 weeks gestation or later in Denmark until 2004. After this period, the National Board of Health changed the definition to the death of a foetus born after 22 completed weeks' gestation. Stillbirth was recorded according to ICD-8 code 779 and ICD-10 code P95. Stillbirth was further categorized into "explained" (antenatal complications, complications of delivery, congenital malformations of the foetus, maternal illness, or injury to the mother) or "unexplained" (unknown causes of death, cancers [including malignant neoplasm of the bone or spinal cord] or other benign neoplasms of



unspecified organs or tissues, post-maturity, and haemorrhages, including co-twin, subarachnoid, other intracranial, newborn, or unspecified haemorrhages. Data on the specific causes of stillbirth were available from 1982–1996 only. Many confounding variables were used to adjust the statistical models but no data were available on known risk factors, including the number of previous sexual partners, history of pelvic inflammatory disease, and age at first intercourse. There were 832 996 first live births, of which 607 252 (72.9%) were SVDs, 38 950 (4.7%) were elective caesareans, and 2 876 (1.1%) were maternally requested caesareans. Of the 832 996 women in the cohort, 1 996 had a subsequent stillbirth, a rate of 2.4 per 1000.

The authors found an increased rate of stillbirth (hazard ratio [HR] 1.14, 95% CI [1.01, 1.28]) in women with primary CS compared to spontaneous VD, giving a theoretical absolute risk increase (ARI) of 0.03% for stillbirth, and a number needed to harm (NNH) of 3 333 women. Analyses by type of caesarean section showed similarly increased rates for emergency (HR 1.15, 95% CI [1.01, 1.31]) and elective caesarean (HR 1.11, 95% CI [0.91, 1.35]), although not statistically significant in the latter case. An additional risks analysis by cause of stillbirth showed an increased rate of explained stillbirth in crude and adjusted models for all caesarean sections combined (HR 1.10, 95% CI [0.89, 1.35]) without reaching statistical significance. In the same way, an increased rate of unexplained stillbirth was found among all caesarean sections combined (HR 1.14, 95% CI [0.76, 1.71]) without being statistically significant. When the indication for CS was analysed, no significant association was found either for prior emergency CS or for prior elective CS. Although the study accounted for a number of important confounders, underlying medical conditions and confounding by indication for the primary caesarean delivery account for at least part of this increased rate.

For the relation between stillbirths in subsequent pregnancies in relation with caesarean section vs. vaginal delivery only observational evidence is available.

One meta-analysis and one primary study report an increased risk for stillbirth in subsequent pregnancies of about 15 to 20%. The heterogeneity between trials in the meta-analysis is extremely high. Consequently, the association could be very dependent on many factors, probably both methodological as well as clinical. Besides, the causal nature of this association is difficult to prove in those observational studies because of the high risk of residual confounding.

**Main conclusion: Overall, compared to vaginal delivery, CS is associated with a small increased rate of subsequent stillbirth. Underlying medical conditions, however, and confounding by indication for the primary CS account for at least part of this increased rate.**



## 11 OVERALL CONCLUSION

### 11.1 Caesarean section: national and international trends

In Europe, CS rates constantly increased over time and in 2010 they varied between 15.6% in The Netherlands and 50% in Greece. In 2010, the CS rate in Belgium was around 20%.<sup>6</sup>

Data over a 20-years period (1987-2007) from 22 industrialised countries are particularly striking.<sup>7</sup> In 2007, 11 of those countries reported overall CS rates of more than 25%, led by Italy (39%), Portugal (35%), the United States (32%), and Switzerland (32%) (Greece was not included in this overview).

In Belgium, CS rates are comparable in the three regions. In 2014 they ranged from 20.4% in the Brussels Region to 22.2% in Wallonia, with 20.6% in Flanders. Remarkable is the large difference across maternity services in all regions, with CS rates ranging from 11.8% to 32.9%. The real reason is not clear, but this may represent differences in case mix or, more likely, differences in practice.

The Robson classification uses ten mutually exclusive categories to group pregnancies. Across the three regions both the global CS rate and the relative contribution of each Robson category is comparable.

Abnormal (transverse or oblique) lies, nulliparous/multiparous breeches and multiple pregnancies are mainly delivered by caesarean section. Globally, these four groups represent about 6% of all pregnancies. **In all three regions, a previous caesarean section is the major indication for a next CS.**

Also notable is the relation between elective and emergency CS. While in Flanders the majority of CS is elective, the proportion of elective and emergency CS in Wallonia and the Brussels region is almost equal. In all Regions, the proportion of elective CS is much higher in multiple births compared to singletons.

### 11.2 Towards an ideal rate of caesarean deliveries?

In 1985, the World Health Organisation (WHO) and the Pan-American Health Organisation (PAHO) held a shared conference on the appropriate technology for birth in Fortaleza, Brazil.<sup>2</sup> The optimal rate for caesarean section (CS) was considered by this international healthcare community to be between 10% and 15%.

In 2015, the WHO issued a statement on CS rates.<sup>3</sup> It starts from the observation that over the last 30 years CS rates gradually increased worldwide, both in developed and in developing countries. Many authorities and clinicians expressed their concerns about this increase and its potential negative consequences. On the other hand, the international healthcare community asked to reconsider the optimal rate proposed in 1985.

At a population level (ecological studies) an increase in CS rate up to 10-15% is associated with a decrease in maternal, neonatal and infant mortality. However, this association weakens or even disappears in studies that control for socioeconomic factors.<sup>3</sup> Above this level of 10-15%, a further increase in CS rate is no longer associated with reduced mortality.

In its statement the WHO concludes that **there is not really an optimal rate**. But, rather than striving to achieve a specific rate every effort should be made to provide CS to women who really need it. It further concludes that CS is effective in saving maternal and infant lives, but only when it is required for medical reasons.



### 11.3 Association between delivery modes and outcomes: level of evidence

In 2012, Lavender et al. attempted to compare the effects on perinatal and maternal morbidity and mortality of planned caesarean delivery versus planned vaginal birth where there is no clear clinical indication for a caesarean section, i.e. in singleton pregnancies with cephalic presentation at term and with no conventional medical indication for caesarean section.<sup>108</sup> Their attempt was unsuccessful and they had to conclude that “there are no randomised controlled trials of planned caesarean section versus planned vaginal birth for non-medical reasons at term. Performing such a randomised controlled trial not only raises methodological concerns but also arouses substantial moral issues about the ethics of undertaking a trial where women randomised to the intervention arm would receive surgery in the absence of a medical indication”.

On the contrary, there have been randomized controlled trials conducted in other situations, in term breech deliveries<sup>39, 109</sup> or in women with a previous caesarean birth.<sup>110</sup> Still, the conclusions of trials on planned caesarean section for medical indications versus planned vaginal birth are not applicable to situations where there are no medical reasons, because caesarean mortality and morbidity is confounded by pre-existing obstetric or general medical conditions.

Therefore, researchers have no other option than to rely on observational studies to formulate recommendations to pregnant women and healthcare practitioners. Observational studies comparing the immediate or long-term effects of delivery methods (caesarean vs. vaginal) abound. To eliminate potential bias, most of them adjust their results by taking into account known confounders, such as maternal age, maternal BMI, maternal smoking behaviour, pre-pregnancy maternal diseases, previous delivery by CS, marital status, parity... In general, paternal potential confounders are not taken into account in those studies. Unfortunately, many other potentially relevant but harder to ascertain confounders are usually not taken into account (e.g. dietary patterns, physical activity, medication use in the studies on overweight and obesity).

Very broad studies involving tens of thousands of women and children and providing very long-term follow-up lead to the conclusion of associations, sometimes very strong, between the delivery method and the health issue studied (maternal or infant morbidity). The most recent and most thorough studies even extend their analysis to siblings and thus compare health issues between brothers and sisters according to their method of birth. Other studies with the same methodological characteristics conclude, on the contrary, that there is no association between the delivery method and the health issues studied. The main weakness of these studies is the inability to reliably report the reason for which a caesarean was performed, thus confusing the delivery procedure with the reason for which it was necessary (health problem of the mother or the child complicating or preventing vaginal delivery).

To date, it therefore remains risky to draw unequivocal conclusions or to establish indisputable causal relationships for most of the issues of maternal and infant health.

### 11.4 Caesarean section: Maternal and offspring outcomes

A caesarean section is a surgical intervention that can prevent mortality and morbidity in both mother and child when performed in situations that really need it. These last years, in industrialised countries, caesarean deliveries have become safe interventions owing to mastered surgical techniques, improved anaesthesia and, the routine use of infection and thrombosis prophylaxis. However, caesarean section remains a surgical procedure with abdominal and uterine incisions, and subsequent scarring and risk of adhesions.<sup>108</sup>

Table 5 summarizes the results of our literature review: some of the clinical consequences are manifest, e.g. the increased risk of future uterine rupture. Most other effects on the short- and long-term are less clear cut and therefore less certain.



Table 5 – Planned caesarean section compared with planned vaginal birth in low-risk pregnant women at term

PLANNED CAESAREAN SECTION COMPARED WITH VAGINAL BIRTH IN LOW-RISK PREGNANT WOMEN AT TERM			
Short-term maternal outcomes			
Planned CS may reduce the risk of:	Planned CS may increase the risk of:	No difference in risk demonstrated:	Inconclusive evidence about increased risk from CS:
Perineal and abdominal pain during birth and 3 days post-partum	Cardiac arrest	Perineal and abdominal pain four months post-partum	Deep vein thrombosis
	Peripartum hysterectomy (after haemorrhage or other complication)	Post-partum haemorrhage and blood transfusion	Wound and postpartum infection
		Injury to bladder/ureter	Anaesthetic complications
		Injury to cervix	Breastfeeding problems
		Injury to vagina	
		Iatrogenic surgical injury	
		Pulmonary embolism	
		Intraoperative trauma	
		Assisted ventilation or intubation	
		Acute renal failure	
		Obstetric shock	
		Maternal mortality	
Long-term maternal outcomes			
Planned CS may reduce the risk of:	Planned CS may increase the risk of:	No difference in risk demonstrated:	Inconclusive evidence about increased risk from CS:
Urinary incontinence		Faecal incontinence	
		Post-natal depression	
Short-term offspring outcomes			
Planned CS may reduce the risk of:	Planned CS may increase the risk of:	No difference in risk demonstrated:	Inconclusive evidence about increased risk from CS:
	Neonatal respiratory problems	Cerebral palsy	Neonatal mortality
Long-term offspring outcomes			
Planned CS may reduce the risk of:	Planned CS may increase the risk of:	No difference in risk demonstrated:	Inconclusive evidence about increased risk from CS:
		Childhood cancer	Respiratory infections
		Developmental and behavioural outcomes	Diabetes mellitus type 1
			Inflammatory bowel disease
			Coeliac disease
			Overweight and obesity
			Asthma
			Atopy
			Gastro-enteritis
			Long-term child mortality
Impact on subsequent pregnancies: maternal and offspring outcomes			
Planned CS may reduce the risk of:	Planned CS may increase the risk of:	No difference in risk demonstrated:	Inconclusive evidence about increased risk from CS:
	Placenta praevia in subsequent pregnancies	Subsequent fertility	Subsequent ectopic pregnancy
	Placenta accreta in subsequent pregnancies		
	Placental abruption in subsequent pregnancies		
	Uterine rupture in subsequent pregnancies		
	Stillbirth in subsequent pregnancies		



### 11.5 Counselling women on the mode of delivery

During the meetings with the expert group, it was repeatedly stressed that women need to be fully, clearly and objectively informed about benefits and consequences of all modes of delivery. Especially the consequences for subsequent pregnancies and future deliveries need to be discussed.

It is clear that in some circumstances a caesarean section is fully justified, but when it comes to caesarean sections 'on maternal request or obstetrician demand' patient information and consent and objective counselling are important. This is also a legal requirement under the law on patient's rights from August 22<sup>nd</sup> 2002.<sup>111</sup> This implies that clear and complete information concerning the whole proposed procedure and its consequences should be delivered to the patient in a clear language understandable by a layperson.

More specifically, the consequences of a first caesarean section should be clearly explained. Although there are a few advantages (less perineal and abdominal pain, lower risk of urinary incontinence) there is also an increased risk of negative consequences for mother and child, including the risk of uterine rupture during a subsequent pregnancy, a very dramatic and life-threatening event for both mother and child.

The international and Belgian data show that a previous caesarean section is the most important driver for a repeat caesarean section in subsequent pregnancies. Future parents should also be made aware of this impact of their current decision.

## 12 EXISTING INITIATIVES

In Belgium, when a child is born, the health care practitioner who performed the delivery has to notify the birth and complete medical data for the Communities and, ultimately, the FPS Economy. These notifications are made either via a paper form or via an electronic application, i.e. e-Birth (since 2010). The e-Birth form allows to record several medical variables very useful for epidemiological studies on previous pregnancies, current pregnancy, delivery (e.g. position at birth, induction, epidural analgesia, fetal monitoring, delivery mode, episiotomy...) or the baby's health status. This form allows to differentiate indications of caesarean section by recording detailed data (maternal indication without additional specification; CS required by the pregnant woman without medical indication; placenta praevia; multiple pregnancy; fetal indication such as dystocia, fetal distress, abnormal position; further indication to be specified). Data related to the hospital (INAMI/RIZIV code of the hospital and of the campus) and the health care practitioner (name, first name, INAMI/RIZIV code) who performed the delivery are also recorded.

Each year the Centre d'Épidémiologie périnatale (CEpiP) and the Studiecentrum voor Perinatale Epidemiologie (SPE) sent to all maternity centers a confidential report containing a feedback related to all obstetric indicators recorded on birth certificates, their evolution since 2008 or 2009 and their positioning relative to other maternity hospitals. This annual report is sent concomitantly with the report by region. These reports are not commented but healthcare professionals who are interested may request a presentation of the results by the research teams, or an electronic version to ensure in-house presentations. It is not an audit of maternity and leaves freedom for practitioners to adapt their practices.

In 2011, the College of Physicians for the mother and the newborn has published a report on the determinants of caesarean rates in Belgium. This report formulated a series of **clinical and organizational recommendations to reduce the number of unnecessary CS**. We refer the interested reader to this publication ([http://overlegorganen.gezondheid.belgie.be/sites/default/files/documents/college\\_van\\_geneesheren\\_voor\\_de\\_moeder\\_en\\_de\\_pasgeborene/190741](http://overlegorganen.gezondheid.belgie.be/sites/default/files/documents/college_van_geneesheren_voor_de_moeder_en_de_pasgeborene/190741)



53.pdf). Authors mentioned that these recommendations have been followed by hospital and private practitioners having an obstetric activity in an academic hospital in 2010, dropping the caesarean rate from 26% to 20.2%. Caesarean section rates related to admission in maternal intensive care (MIC) was unchanged. This illustrates that the observed decrease was almost exclusively due to the reduction of caesarean sections performed on low-risk pregnant women.



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