

Intrahepatic Cholestasis of pregnancy

DATA COLLECTION FORM

STUDY - IDENTIFICATION NUMBER: **ICP000**

**BACKGROUND INFORMATION**

Intrahepatic Cholestasis of Pregnancy (ICP) affects 0.1–2% of pregnant women. Its incidence is higher in some countries, such as Chile and Norway (1). ICP is diagnosed in women with gestational pruritus and increased levels of serum bile acids, and can be complicated by preterm labor, fetal asphyxia, meconium-stained amniotic fluid, and stillbirth (2). It is associated with maternal discomfort because of pruritus and it can be associated with insomnia and general symptoms (3). According to retrospective studies, the increased risk of stillbirth is associated with high maternal serum bile acid concentrations (4). A large 2019 meta-analysis demonstrated that bile acid levels above 100 micmol/L were associated with a significant increased risk of stillbirth, 30-50 times higher than when bile acid levels were <100 micmo/L (5). The risk of stillbirth increases with increasing gestational age. The meta-analysis showed no increase in stillbirth compared to the background population before 39 weeks gestation when bile acids were <100 micmol/L. However, it is important to notice that the high number of iatrogenic preterm birth may have biased these numbers. It seems that ursodeoxycholic acid (UDCA) is effective against pruritus (6), but it is not clear whether ursodeoxycholic acid reduces neonatal morbidity and mortality. The recent PITCHES study (a double-blind, multicenter, randomized placebo-controlled trial at 33 hospital maternity units in England and Wales) showed that the treatment with UDCA does not reduce adverse perinatal outcomes, in women affected by ICP, and suggest reconsidering its routine use for this condition (7). There is no standard management for ICP (8): there is no strong evidence that monitoring by US or cardiotocogram can reduce adverse fetal outcomes (2). There is no consensus on bile acid level dosage, or on the right gestational age for termination of the pregnancy (8, 9, 10). As a result of the above key points, there is scope for improvement in the outcome of ICP through a better understanding and awareness of the problem

With this study we want to investigate intermediate (bile acids 40-99 micmol/L) and severe (bile acids ≥ 100 micmol/L) ICP in Belgium: to determine the incidence of this pregnancy complication, the diagnosis and management in Belgian hospitals and the maternal and fetal outcomes of pregnancies complicated with ICP. Further, we want to compare Belgian incidence, management and outcome of ICP with our neighbouring countries.

1. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2014;124(1):120–33.
2. Herrera CA, Manuck TA, Stoddard GJ, et al. Perinatal outcomes associated with intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med. 2018; 31(14): 1913–1920.
3. Geenes V, Williamson C, Chappell LC. Intrahepatic cholestasis of pregnancy. The Obstetrician & Gynaecologist 2016;18:273–81
4. Glantz A, Marschall HU, Mattsson LA: Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology. 2004, 40: 467-474. 10.1002/hep.20336.
5. Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet. 2019;393(10174):899-909
6. Chappell LC, Gurung V, Seed PT, Chambers J, Williamson C, Thornton JG. Ursodeoxycholic acid versus placebo, and early term delivery versus expectant management, in women with intrahepatic cholestasis of pregnancy: semifactorial randomised clinical trial. *BMJ.*2012;344:e3799.
7. Chappell LC, Bell JL, Smith A, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. Lancet 2019; 394:849.
8. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: Review of six national and regional guidelines, [European Journal of Obstetrics & Gynecology and Reproductive Biology](https://www.sciencedirect.com/science/journal/03012115), [Volume 231](https://www.sciencedirect.com/science/journal/03012115/231/supp/C), December 2018, Pages 180-187
9. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 560: Medically indicated late-preterm and early-term deliveries. Obstet Gynecol. 2013;121:908–910
10. Royal College of Obstetricians & Gynaecologists. Obstetric Cholestasis (Green Top Guidelines n°43). Accessed online October 2019 via <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg43/>.

**CASE DEFINITION**

Every pregnant woman identified as having

**Intermediate** (bile acids 40-99micmol/L) or **Severe**  (bile acids ≥ 100micmol/L)

**Intrahepatic Cholestasis of Pregnancy (ICP)**

Defined as:

* Pruritus without rash associated with elevated serum bile acid levels ≥ 40 micmol/L
* At any stage of the pregnancy,
* Not explained by other pathologies,
* Disappearing after the delivery.

**Exclusion criteria:**

* Serum bile acid levels less than 40 micmol/L
* Other hepatic/infectious/dermatologic/pregnancy disease, which could explain the symptoms

**DATA COLLECTION FORM**

### Section 1. Woman’s details

* 1. Year of birth: (YYYY) 0000
  2. Country in which patient was born
  3. Is the mother single?

Yes

No

Not known

* 1. Did the patient or her partner have a steady income during pregnancy (excluding social security)

Yes

No

Not known

* 1. Height at 1st visit:      cm
  2. Weight at 1st visit:      kg
  3. ~~Calculate BMI:~~ ~~kg/m~~~~2~~
  4. Did the patient smoke during pregnancy? (answer yes, even if she quit during pregnancy)

Yes

No

Not known

* 1. What was the highest education of the patient?

|  |
| --- |
| no formal schooling |
| Less than primary schooling |
| Primary school |
| Secondary school |
| Higher: bachelor, master, university |
|  |

### Section 2. Previous Obstetric History

* 1. Gravidity.
     1. Number of current pregnancy (number)
     2. Number of completed pregnancies of ≥ 22 weeks (number)
  2. Please indicate if any of the following were present in previous pregnancies:

|  |
| --- |
| Gestational diabetes |
| Pre-eclampsia |
| HELLP syndrome |
| ICP |

* 1. If the patient had previous ICP
     1. At which gestational age did it appear? (number of weeks)
     2. At wich gestational age did she deliver (number of weeks)
     3. Did she experience (tick all that apply)

|  |
| --- |
| Spontaneous preterm labour  Fetal asphyxia  Meconium-stained amniotic fluid  Stillbirth |

* 1. Did the woman have any other previous pregnancy problems?

Yes

No

If yes, please specify

Recurrent miscarriages (3 or more)

Amniocentesis

Amniotic fluid embolism

Baby with a major congenital abnormality

Haemorrhage

Infant requiring intensive care

Neonatal death

Ovarian hyperstimulation syndrome

Placenta praevia

Placental abruption

Post-partum haemorrhage requiring transfusion

Pre-eclampsia (hypertension and proteinuria)

Premature rupture of membranes

Partus prematurus

Partus immaturus

Puerperal psychosis

Severe infection e.g. pyelonephritis

Stillbirth

Surgical procedure in pregnancy

Other, please specify

### Section 3. Previous personal and familiar medical history

* 1. Was there a previous or pre-existing maternal medical condition?

Yes

No

Not known

If yes, please specify

Cardiac disease (congenital or acquired)

Diabetes

Epilepsy

Endocrine disorders e.g. hypo or hyperthyroidism

Essential hypertension

Haematological disorders e.g. sickle cell disease

Inflammatory disorders e.g. inflammatory bowel disease

I.V. drug use

Lung disease

Myeloproliferative disorders e.g. essential thrombocythaemia, polycythaemia vera

Neoplasia

Paraplegia

Psychiatric disorders

Renal disease e.g. nephrotic syndrome

Systemic lupus erythematosus

Other, please specify

* 1. Any previous surgery (including caesarean section)

Yes

No

Not known

If yes, please specify

* 1. Please indicate whether any of the following specific problems: (tick all that apply)

Hepatitis C infection   
 Hepatitis B infection   
 Hepatitis A infection   
 Ebstein Barr Virus infection   
 Cytomegalovirus infection   
 Autoimmune Hepatitis   
 Primary biliary cirrhosis

Primary sclerosing cholangitis   
 Gallstone   
 Cyclical itch/cholestasis  
 Other episode of cholestasis, like drug induced

* 1. Did anybody of the family experienced ICP during a previous pregnancy?

Yes

No

Not known

If yes specify relation to the patient

### Section 4: This pregnancy

* 1. The number of foetuses in current pregnancy (≥ 22 weeks)
  2. Gestational age in completed weeks at booking (first antenatal visit)
  3. Beginning of the pregnancy

Spontaneous   
 Hormonal

IVF/ICSI

Not known

* 1. Is this pregnancy complicated by

Gestational Diabetes  
 Pregnancy Induced Hypertension

Preeclampsia   
 Hyperemesis of the first trimester

* 1. Gestational age at the diagnosis of ICP (number of completed weeks)
  2. Did the mother suffer from the following symptoms

(at the time of diagnosis or any time following diagnosis)

|  |  |  |
| --- | --- | --- |
|  | Yes | GA at onset |
| Pruritus |  |  |
| Vomiting |  |  |
| Abdominal pain |  |  |
| Insomnia |  |  |
| Jaundice |  |  |
| Steatorrhea |  |  |
| Hypoglycaemia |  |  |

* 1. Was abdominal US performed

Yes

No

If yes, what were the findings

* 1. Were other imaging techniques performed?

Yes

No

Not known

If yes, what type of imaging technique?

If yes, what were the findings

* 1. Was a liver biopsy performed?

Yes

No

Not known

If yes, what were the findings

* 1. Please note if any other problems of the pregnancy occurred?

Amniocentesis

Antenatal haemorrhage

Ovarian hyperstimulation syndrome

Placenta praevia

Placental abruption

Premature rupture of membranes

Puerperal psychosis

Severe infection e.g. pyelonephritis

Surgical procedure in pregnancy

Other, please specify

### Section 5. Biochemistry before delivery

**5.1.** Please mark the level at diagnosis, the worst recorded level and the level at delivery

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | At diagnosis | Worst level + GA at worst level | | At delivery |
| Serum bile acids (micmol/L) |  |  |  |  |
| AST (U/L) |  |  |  |  |
| ALT(U/L) |  |  |  |  |
| Bilirubin (mg /dL) |  |  |  |  |
| GGT (U/L) |  |  |  |  |
| Creatinine (mg/dL) |  |  |  |  |
| Platelets (x103 mm3) |  |  |  |  |
| PT (%) |  |  |  |  |
| APTT (s) |  |  |  |  |
| WBC count (x103 mm3) |  |  |  |  |

* 1. Please note how the sample type of bile acid level was taken

|  |
| --- |
| Fasten   Random  Not known |

### Section 6. Treatment

* 1. Was treatment with ursodeoxycholic acid (UDCA) started?

Yes

No

* 1. If yes please give the dose (total daily dose in mg)       and gestational age (in completed weeks) at start treatment
  2. Did symptoms improved with UDCA?

Yes , Please specify which symptoms:

No

Not known

* 1. How often were bile acids measured?

More than 1xweek

Weekly

Every two weeks

Less than every two weeks

* 1. How long does it take for the results of bile acids to come back in your maternity?

Less than 24 hours

24 to 48 hours

More than 48 hours

* 1. How do you usually control bile acids in pregnant patients in your maternity unit?

Fasted

Random

* 1. Was treatment with K vitamin started?

Yes

No

* 1. Did the woman receive treatment for fetal lung maturation?

Yes

No

If yes at what GA? (number of completed weeks)

* 1. Was any other treatment started?

Yes

No

If yes, please specify

### Fetal monitoring

* 1. How often was a fetal US performed?

More than once per week

Once per week

Once every 2 weeks

Less than once every 2 weeks

* 1. Were any foetal US abnormalities recorded?

Yes

No

If yes, Please specify

* 1. How often was a cardiotocography performed

More than once per day

Once per day

More than once per week

Once per week

Less than once per day

None

* 1. Were any CTG abnormalities recorded?

Yes

No

N/A

If yes, Please specify

* 1. Were any other monitoring strategy employed? (eg. Home monitoring, Kick chart, …)

Yes

No

If yes please specify

* 1. Was the patient admitted to the hospital in this pregnancy (besides hospitalisation for delivery)?

Yes

No

If yes, at what GA was she admitted (number of completed weeks)?

If yes, was she admitted for fetal monitoring because of ICP

Yes

No

If no, please specify the reason for admission:

### Section 8. End of pregnancy

* 1. Gestational age in completed weeks at the end of the pregnancy
  2. What was the planned mode of delivery?

Vaginal

Caesarean section

* 1. Was delivery induced?

Yes

No

If yes:

* + 1. Please specify the reason for the induction
    2. The method of the induction (more than one option possible)

Amniotomy

Oxytocin

Prostaglandin IV

Prostaglandin vaginal/intra-cervical

Catheter balloon

Double balloon

* 1. Did the woman labour?

Yes

No

If yes :

* + 1. Was labour augmented?

Yes

No

If yes, please specify augmentation methods:

Amniotomy was performed for augmentation

Oxytocin was used for augmentation

* + 1. What type of monitoring was performed?

Continuous cardiotocography

STAN monitoring

Intermittent cardiotocography

Were any CTG abnormalities / STAN events recorded during labor?

Yes

No

N/A

If yes, please describe

* + 1. If yes please specify:

The length of the 1st stage of labour (number of hours)

The length of the 2nd stage of labour (number of minutes)

* 1. Mode of delivery 1st neonate

Spontaneous cephalic

Breech

Instrumental vaginal delivery

Pre-labour caesarean section

Secondary caesarean section

In case of caesarean section, please specify

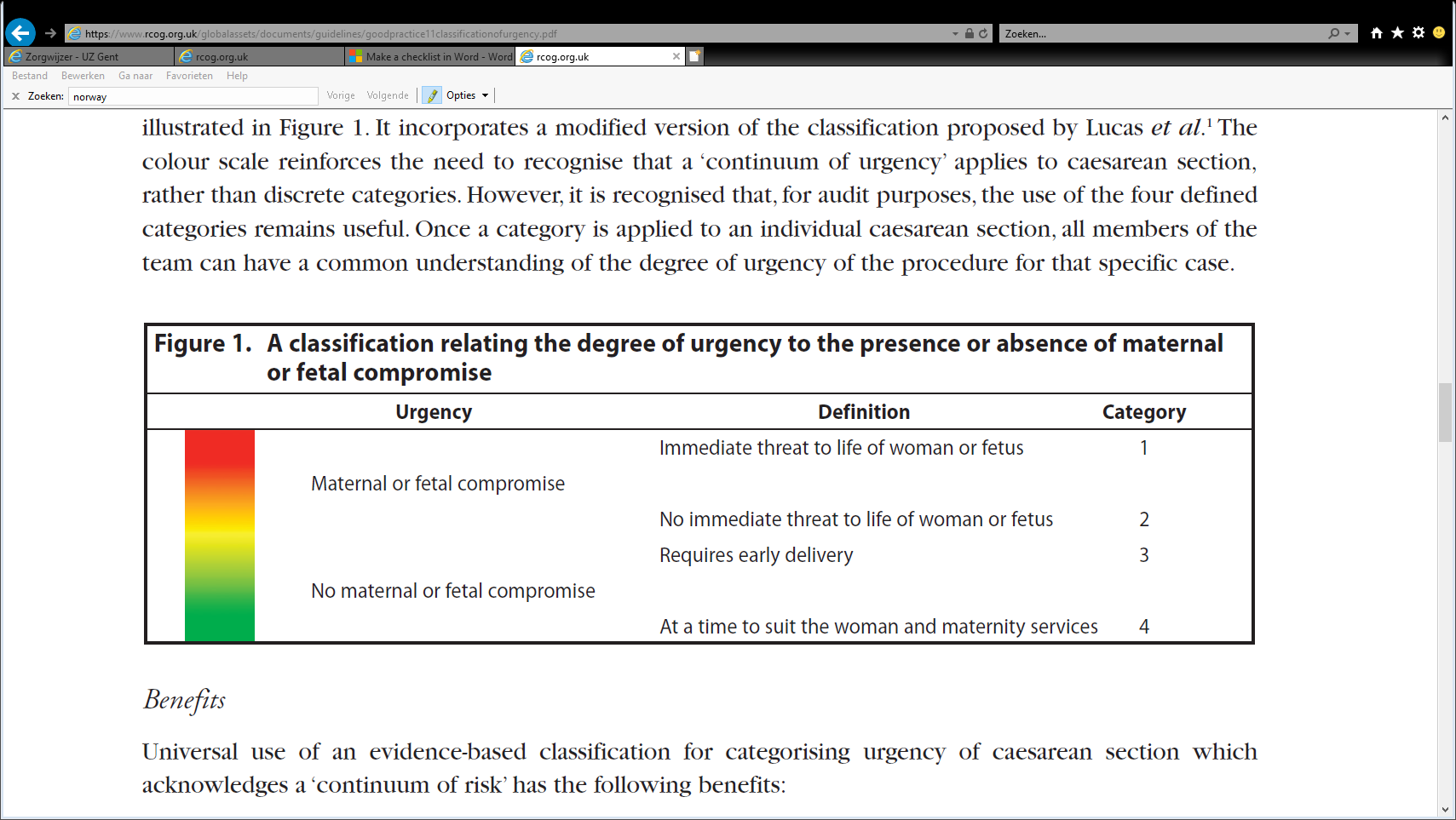
* + 1. Reason for caesarean section

Maternal

Fetal   
Elective

Please specify      

* + 1. Grade of urgency



Category I

Category II

Category III

Category IV

* 1. Type of analgesia

General

Loco-regional

None

* 1. In case of twin pregnancy – based on question 4.1
     1. Mode of delivery 2nd neonate

Spontaneous cephalic

Breech

Instrumental vaginal delivery

Pre-labour caesarean section

Secondary caesarean section

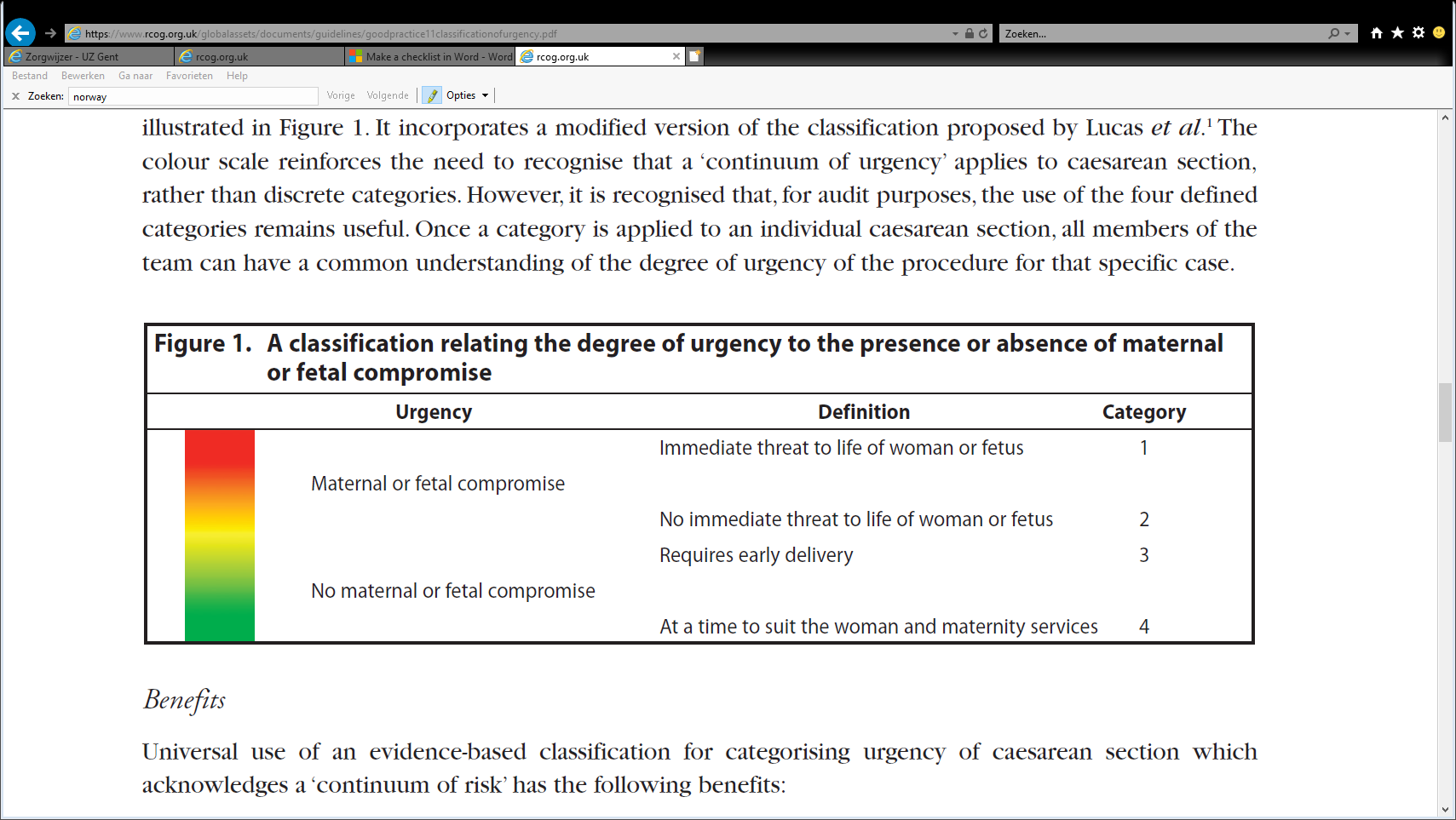
* + 1. In case of caesarean section, please specify reason for caesarean section

Maternal

Fetal   
Elective

Please specify      

* + 1. Grade of urgency



Category I

Category II

Category III

Category IV

* 1. Type of analgesia

General

Loco-regional

None

* 1. How was the placenta delivered?

Spontaneous  
 Manual

* 1. Was the placenta analysed?

Yes , Please specify diagnosis:

No

N/A

### Section 9. Maternal outcomes

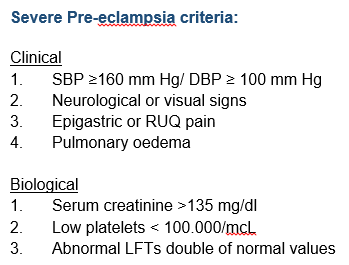
* 1. Did any major maternal morbidity occurred:

Post-partum haemorrhage

If yes: estimated blood loss in ml

If yes: number of Packed Cells transfused

Severe pre-eclampsia (See list 4: definition of severe preeclampsia)



Admission to Intensive care unit / high depency unit

If yes: how many days        
If yes: reason for admission

* 1. Did the mother die

Yes

No (Please go straight to section 10)

* + 1. If yes, please specify the timing of death following birth

< 24 hours

< 7 days

< 42 days

> 42 days

* + 1. If yes, what was the cause of death?
    2. If yes, was postmortem performed

Yes

No

*If yes*, please specify diagnosis

### Section 10. Infant outcomes

(please complete one section for each infant)

* 1. Birthweight       grams
  2. Percentile
  3. Sex of the infant

male

female

indeterminate

* 1. Was the infant stillborn

Yes

No (Please go straight to 10.4.2)

* + 1. **If yes** : please complete this part 10.4.1 and go to Section 11

Cause of death (if known):

Gestational age at diagnosis       completed weeks

Last US before diagnosis of stillbirth       days before

Last cardiotocography before diagnosis of stillbirth       days before

Was postmortem performed

Yes , please specify diagnosis

No

Please add any other relevant details:

* + 1. **If not stillborn** :

1. min Apgar

Was the infant admitted to neonatal unit?

Yes

No

If yes, please complete

How many days?

Indication for admission

Was there meconium-staining of the amniotic fluid, placenta or membranes?

Yes

No

N/A

Was the umbilical arterial or venous pH measured?

Yes

No

If yes please complete the values:

Arterial pH       BE         
Venous pH       BE

Did any major neonatal complication occur? (see list number 5)

Yes

No

If yes please specify (list 5)

Chronic lung disease

Exchange transfusion

Intraventricular haemorrhage

Jaundice requiring phototherapy

Necrotising enterocolitis

Neonatal encephalopathy

Respiratory distress syndrome

Severe infection e.g. septicaemia, meningitis

Other, please specify

Did the infant have any congenital anomaly?

Yes

No

If yes please specify (free text)

Did the infant die?

Yes

No (Please go straight to section 11)

If yes please specify:

Timing of death

<24 h

< 7d

< 28d)

Was postmortem performed

Yes , please specify diagnosis

No

### Section 11. Post partum

* 1. Were the serum bile acid levels controlled after the delivery?

Yes

No

If yes, how many weeks after?

Value of BA in the Post partum?      micmol/L

* 1. Was there further follow-up of this woman by a liver specialist ?

Yes

No

If yes, please specify findings if any

* 1. Did the patient receive any contraception after the delivery?

N/A

Yes

No

Not known

If yes, please specify:

Oral estrogen-progestin pills  
Oral progestin pills  
Progestin IUD   
Non-hormonal IUD  
Progestin implant  
Other EP methods   
Barrier methods

### Section 12. Any other remarks

* 1. Please note any other remarks you have regarding this case:

Finished

Please check this box when you are finished with this form.

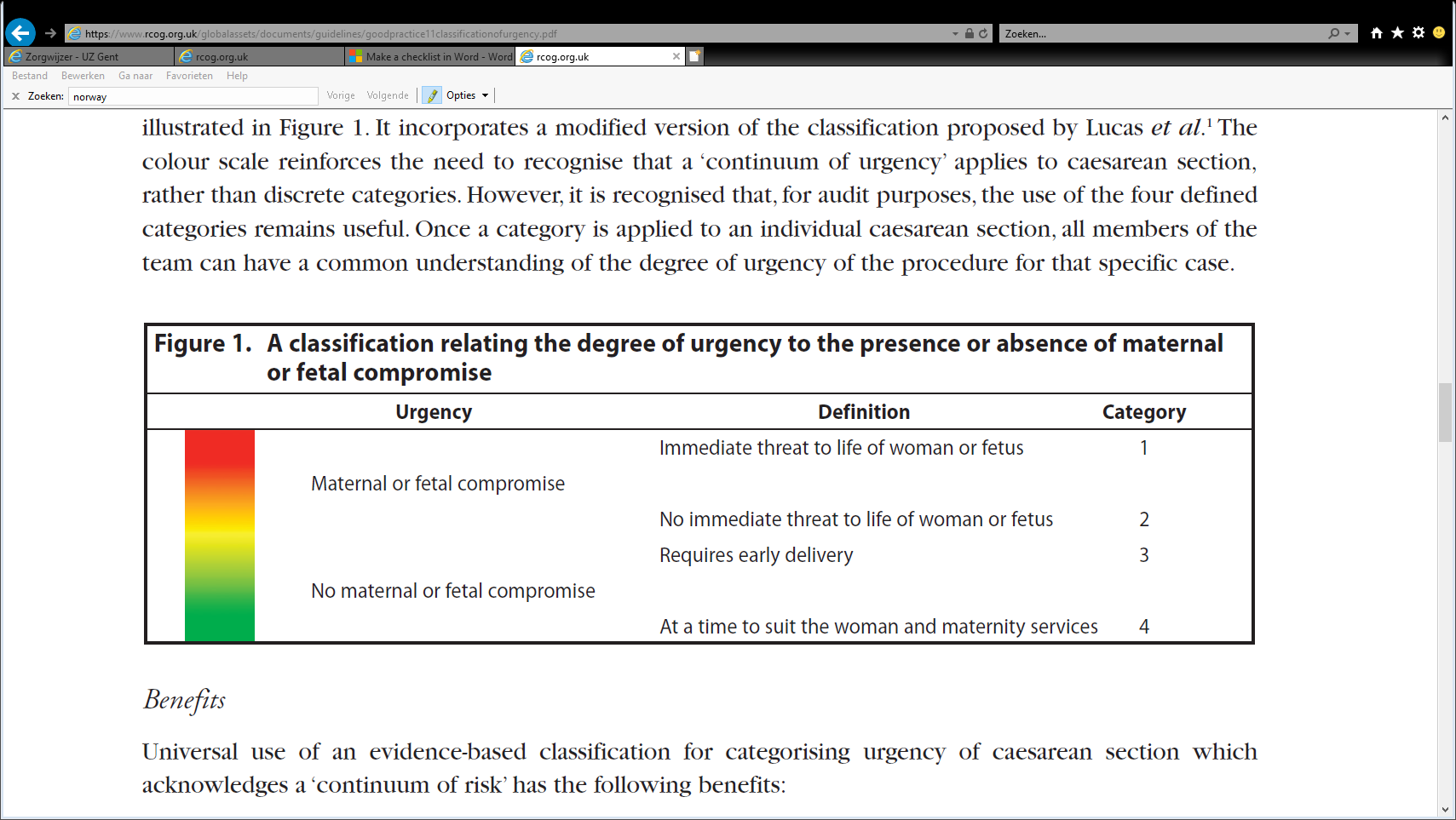
##### **List 1: Previous or current pregnancy problems, including**

1. Recurrent miscarriages (3 or more)
2. Amniocentesis
3. Amniotic fluid embolism
4. Baby with a major congenital abnormality
5. Gestational diabetes
6. Haemorrhage
7. Hyperemesis requiring admission/ Dehydration
8. Infant requiring intensive care
9. Neonatal death
10. Ovarian hyperstimulation syndrome
11. Placenta praevia
12. Placental abruption
13. Post-partum haemorrhage requiring transfusion
14. Pre-eclampsia (hypertension and proteinuria)
15. Premature rupture of membranes
16. Partus prematurus
17. Partus immaturus
18. Puerperal psychosis
19. Severe infection e.g. pyelonephritis
20. Stillbirth
21. Surgical procedure in pregnancy
22. Other, please specify

##### **List 2: Previous or pre-existing maternal medical problems, including**

1. Cardiac disease (congenital or acquired)
2. Diabetes
3. Epilepsy
4. Endocrine disorders e.g. hypo or hyperthyroidism
5. Essential hypertension
6. Haematological disorders e.g. sickle cell disease
7. Inflammatory disorders e.g. inflammatory bowel disease
8. I.V. drug use
9. Lung disease
10. Myeloproliferative disorders e.g. essential thrombocythaemia, polycythaemia vera
11. Neoplasia
12. Paraplegia
13. Psychiatric disorders
14. Renal disease e.g. nephrotic syndrome
15. Systemic lupus erythematosus

##### **List 3: Previous or pre-existing maternal medical problems, including**



##### **List 4: Severe Pre-eclampsia criteria:**

Clinical

1. SBP ≥160 mm Hg/ DBP ≥ 100 mm Hg
2. Neurological or visual signs
3. Epigastric or RUQ pain
4. Pulmonary oedema

Biological

1. Serum creatinine >135 mg/dl
2. Low platelets < 100.000/mcL
3. Abnormal LFTs double of normal values

##### **List 5: Infant complications, including:**

1. Chronic lung disease
2. Exchange transfusion
3. Intraventricular haemorrhage
4. Jaundice requiring phototherapy
5. Major congenital anomaly
6. Necrotising enterocolitis
7. Neonatal encephalopathy
8. Respiratory distress syndrome
9. Severe infection e.g. septicaemia, meningitis
10. Other, please specify