Collège de Médecins "pour la Mère et le Nouveau-Né"
College van Geneesheren "voor de moeder en pasgeborene"

2012 Rapport- Section maternité

Le programme de recherche développé a comporté 3 volets :
1. Définition de critères d'admission et de référence, choix de critères objectifs permettant d'évaluer l'activité au sein des Maternal Intensive Care
2. Registry and surveillance of rare complications in pregnancy
3. National register for epidemiological record, concerted management related to rare gestational trophoblastic diseases.

**Définition de critères d'admission et de référence,
choix de critères objectifs permettant d'évaluer
l'activité au sein des Maternal Intensive Care**

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1. Introduction

The MIC (Maternal Intensive Care) beds are designed to allow intensive observation and care of patients whose pregnancy is at high risk, of women who require highly specialized care after delivery, or whose babies require intensive care after birth. Since 1996, 18 of the 106 Belgian maternity wards are equipped with MIC beds and a neonatal intensive care service. The number of MIC beds is independent of the size of the maternity and varies between 8 and 20 by maternity. In practice, MIC beds do not constitute a separate setting but are embedded in a maternity setting and are eligible for additional funding that strengthens the team of midwives specialized in the care of high risk pregnancy. The law has not detailed the indications for admission to a MIC bed. Therefore large variations exist between hospitals in terms of admission and referral policy. According to the KCE report of 2008, only 40% of patients with high-risk pregnancy are actually admitted to a MIC.

Tools to determine the level and quality of MIC activity lack as well as tools to evaluate the operational functioning of the MIC centers in terms of meeting criteria for MIC admission, transfer and re-transfer. That's why the College Mother and Newborn wishes to select indicators of quality of MIC.

2. Methodology

Delphi Method

For this purpose the Delphi Method was chosen
The Delphi Method is a
    - Qualitative research technique but with quantitative elements

- Gives mean and standard deviation
- Relies on the judgement of a formed panel of experts
- Iterative process with continuous feed back of the responses, until consensus
- The objective is to help a panel of experts to define consensual opinion.

The different steps are (http://semato.uqam.ca/guidexpert-ato/ss.asp)
- First : to establish themes (collect from the experts, the potential indicators to be assessed)
- Second : to assess themes and place in rank order (all experts receive the list of potential indicators and attribute to each a validation score and a feasibility score).
- The system extracts results, the median scores are calculated and recorded on the website visible for all participants.
- Third : assess ranking and re-rank continuously (All experts come back on the website and re-evaluate their first assessment taking into account the opinion of the others).

An Academic Research Department in Montreal University *(Pierre Plante Ph.D., Analyste informatique, Faculté des Sciences Humaines, Université du Québec à Montréal)* was contacted for this purpose.

MIC subgroup

Within the College Mother Newborn a MIC subgroup was established: Sophie Alexandre, Bart Bollen, Jean-Luc Deville, Roland Devlieger, Jean- Michel Foidart, Anne Loccufier, Marleen Temmerman and Kristien Roelens (chair).

After several meetings the working group came up with a list of potential quality indicators for MIC, organised in 'structure', 'procedure' and 'outcome'. For each indicator it was asked to assess validity (score 1-5) and feasibility (score 1-5). An indicator was considered feasible or valid when the median score was ≥4.

In January 2012 the electronic inquiry was sent to all members of the MIC subgroup as test phase. No major modifications took place.

Questionnaire

Quality of the respondent		
You are answering this questionnaire in your quality of		
Head of MIC or his/her delegate		
Head of NIC or his/her delegate		
Head of maternity without P* or his/her delegate		
Head of maternity with P* or his/her delegate		
Besides, you are		
College Mother New Born Member		
Expert for College Mother New Born		
Representative of GGOLFB/VVOG scientific societies to the College		
Number of deliveries in the maternity in 2010	0-500	
	501-1000	

	1001-1500	
	1501-2000	
	over 2000	
STRUCTURE : How should a MIC environment be equipped and how staff should be available ?	Validity	Feasability
Neonatal Intensive Care Unit in same hospital	scale 1 to 5	scale 1 to 5
Intensive Care Unit in same hospital	scale 1 to 5	scale 1 to 5
Operating Room in labor ward	scale 1 to 5	scale 1 to 5
Interventional radiology in same hospital	scale 1 to 5	scale 1 to 5
Blood bank in same hospital	scale 1 to 5	scale 1 to 5
Clinical and molecular Genetics service in hospital	scale 1 to 5	scale 1 to 5
Fetal pathology service in hospital	scale 1 to 5	scale 1 to 5
24h/24h availability of trained midwives in MIC	scale 1 to 5	scale 1 to 5
24h/24h availability of competent MIC OB/GYN (on call)	scale 1 to 5	scale 1 to 5
24h/24h availability of competent MIC OB/GYN (in hospital)	scale 1 to 5	scale 1 to 5
24h/24h availability of anesthesiologists in hospital	scale 1 to 5	scale 1 to 5
24h/24h availability of anesthesiologists trained in high risk obstetrics	scale 1 to 5	scale 1 to 5
24h/24h availability of surgical team to handle all major obstetrical complications	scale 1 to 5	scale 1 to 5
24h/24h availability of neonatologists	scale 1 to 5	scale 1 to 5
Capacity to perform 3th level Ultrasound	scale 1 to 5	scale 1 to 5
Capacity to do Invasive Prenatal Diagnostics	scale 1 to 5	scale 1 to 5
Possibility of fellowship in maternal-fetal medicine in hospital	scale 1 to 5	scale 1 to 5
MIC PROCEDURES AND ORGANISATION		
Multidisciplinary staff meeting daily	scale 1 to 5	scale 1 to 5
Multidisciplinary staff meeting weekly	scale 1 to 5	scale 1 to 5
Multidisciplinary staff meeting monthly	scale 1 to 5	scale 1 to 5
Availability of locally adapted guidelines	scale 1 to 5	scale 1 to 5
Availability of locally adapted guidelines to the referring centers	scale 1 to 5	scale 1 to 5
Regular contact between referring and referral centers for a specific patient by phone	scale 1 to 5	scale 1 to 5
Regular contact between referring and referral centers for a specific patient by e-mail	scale 1 to 5	scale 1 to 5
Regular contact between referring and referral centers for a specific patient by letter	scale 1 to 5	scale 1 to 5
Level of doctors in MIC referral center responding to phone calls from referring center	scale 1 to 5	scale 1 to 5
Level of doctors in MIC referral center who first see the transferred patients	scale 1 to 5	scale 1 to 5
OUTCOME OF MIC ACTIVITIES		
Scientific output: mean number of national publications per year in the past 5 years	scale 1 to 5	scale 1 to 5
Scientific output: mean number of international publications per year in the past 5 years	scale 1 to 5	scale 1 to 5
Permanent education of medical staff	scale 1 to 5	scale 1 to 5

Permanent education of midwifery staff	scale 1 to 5	scale 1 to 5
Number of intrauterine transfers (IUT) to P* function per year	scale 1 to 5	scale 1 to 5
Number of postpartum transfers to P* function per year (maternal or neonatal)	scale 1 to 5	scale 1 to 5
Number of refused transfers per year	scale 1 to 5	scale 1 to 5
(number of demands for transfer to MIC unit that could not be accepted due to practical reasons (eg no place in NIC unit))		
Number of retransfers per year	scale 1 to 5	scale 1 to 5
Percentage of retransfers per year	scale 1 to 5	scale 1 to 5
(number of retransfers per year*100 / number of IUT per year)		
Number of patients transferred from Intensive Care Unit to MIC or from MIC to Intensive Care Unit per year	scale 1 to 5	scale 1 to 5
Number of deliveries of patients already referred to MIC facility during prenatal outpatient care per year	scale 1 to 5	scale 1 to 5
MIC Mean Occupancy rate	scale 1 to 5	scale 1 to 5
(% of MIC beds with MIC pathology = number of MIC patients/number of MIC beds/day)		
Number of admissions of MIC patients per year	scale 1 to 5	scale 1 to 5
Number of MIC patients per year	scale 1 to 5	scale 1 to 5
Number of births < 28 weeks per year	scale 1 to 5	scale 1 to 5
Number of births < 32 weeks per year	scale 1 to 5	scale 1 to 5
Number of births < 34 weeks per year	scale 1 to 5	scale 1 to 5
Number of babies with birth weight < 1000 g per year	scale 1 to 5	scale 1 to 5
Number of babies with birth weight < 1500 g per year	scale 1 to 5	scale 1 to 5
Number of babies > 22 weeks with congenital abnormalities per year	scale 1 to 5	scale 1 to 5
Number of babies > 22 weeks with congenital abnormalities who need Neonatal Intensive Care and/or surgery per year	scale 1 to 5	scale 1 to 5
Number of invasive prenatal procedures (intra-uterine transfusions, laser coagulation, foetal surgery) per year	scale 1 to 5	scale 1 to 5
Number of Preeclampsia/HELLP/acute fatty liver of pregnancy < 34 weeks per year	scale 1 to 5	scale 1 to 5
Number of deliveries of mothers with severe psychopathology requiring hospitalisation per year	scale 1 to 5	scale 1 to 5
Number of deliveries of severely ill mothers (severe astma, liver failure, renal failure, severe heart disease, sickle cell anemia …) per year	scale 1 to 5	scale 1 to 5
Number of severe Obstetrical Complications or 'near-miss' events (eclampsia, uterine rupture, peripartum hysterectomie or embolisation of uterine vessels) per year	scale 1 to 5	scale 1 to 5

Participants

The list of participants was obtained from SPE and CEpiP. It included Heads of Gynecology-Obstetrics Departments (maternities with and without P*, 104), Heads of MIC (18), Heads of NIC (19) as well as participants to the College. Since participants may endorse two responsibilities (head of MIC is more likely to be head of maternity), the number of participants was 130.

After an official contact, the email addresses was updated. Hence, 2 email addresses of heads of maternities couldn't be determined after several actions. The list of the final 128 contacted participants was as follows :

acorremans@mznl.be
alain.vanpeperstraete@gmail.com
ann.verougstraete@pandora.be
anne.godart@cmsenamur.be
anne.loccufier@telenet.be
Anne-Britt.JOHANSSON@huderf.be
Anne-Marie.Dieltjens@GZA.BE
bart.vanovermeire@erasme.ulb.ac.be
beatrice.thaler@pandora.be
bellens.anne@pandora.be
bollenbart@telenet.be
christian.debauche@uclouvain.be
christian.gautier@cndg.be
ckirkpat@ulb.ac.be
Claire.Theyskens@zol.be
coppensmarc@skynet.be
dallequinmc@hotmail.com
danielaburrini@skynet.be
didier.oberweis@chu-charleroi.be
direction.maternite.seraing@chbah.be
dominique.rodez@chrnamur.be
dominique_haumont@stpierre-bru.be
dominiqueleleux@skynet.be
doucetfabrice@yahoo.fr
dr.claudot@skynet.be
dr.g.vlaemynck@skynet.be
dr.harry.coppens@azstdimpna.be
elisabeth.henrion@chr-namur.be
els.desmedt@pandora.be
eric.cavatorta@chu-charleroi.be
erik.eulaers@skynet.be
ewald.goenen@mail.chrvs.be
fbleus@yahoo.fr
filip.cools@uzbrussel.be
Francois.GUILMOT@entitejolimontoise.be
Frank.mestdach@vzwgo.be
frankvermeersch@skynet.be
frans.wesling@zna.be
frederic.debieve@uclouvain.be
frederic.kridelka@chu.ulg.ac.be
geert.luyckx@sjki.be
geert.page@skynet.be
georgey@skynet.be
guidopannemans@belgacom.net
gunnar.naulaers@uzleuven.be
guy.vanneste@pandora.be
hedwig.trappeniers@telenet.be
henk.loobuyck@azstlucas.be

Hilde.Vandebroek@zna.be
hildeverlaenen@skynet.be
ignace.vergote@uzleuven.be
ine.riphagen@rztienen.be
isajaumain@hotmail.com
jaak.waignein@pandora.be
jacqueline.greindl@skynet.be
jacques.caprasse@cha.be
jacques.francotte@skynet.be
jacques.jani@chu-brugmann.be
jan.van.den.haute@olvz-aalst.be
je.verougstraete@clinique-saint-pierre.be
jean.renard@gza.be
jeanlucdeville@hotmail.com
jean-michel.mine@hdc.be
jmfoidart@ulg.ac.be
johan.vanwiemeersch@gza.be
johanvanginderachter@pandora.be
jp.nyssen@hospital-eupen.be
Julie_belhomme@Stpierre-bru.be
KRISTIEN.ROELENS@UGent.be
lecart.chantal@ghdc.be
leonardo.gucciardo@chu-brugmann.be
louise.masters@scarlet.be
luc.cornette@azsintjan.be
luc.verheyen@skynet.be

LVanderVoort@hhr.be
M.Bafort@hhk-eeklo.be
marc.flausch@chirec.be
marc.horion@skynet.be
marc.marechal@chu-charleroi.be
marc.wayembergh@chwapi.be
marleen.temmerman@UGent.be
michelle.nisolle@chrcitadelle.be
mieke.geyskens@azherentals.be
mullermf@yahoo.fr
muriel.romain@skynet.be
myriam.hanssens@uz.kuleuven.ac.be
naschockaert@skynet.be
pascale.grandjean@chr-afic.be
patricia_barlow@stpierre-bru.be
patrick.emonts@chu.ulg.ac.be
Patrick.Van.Reempts@uza.be
paul.befahy@tristare.be
paul.deschilder@skynet.be
paul.viaene@skynet.be
paulcorveleyn@hotmail.com
philip.lebrun@telenet.be
philippe.delattin@imelda.be
philippe.petit@chrcitadelle.be
Pierre.Bernard@uclouvain.be
pierre.leblicq@hap.be

pierre.maton@chc.be
piet.vanhaesebrouck@ugent.be
r.buts@chmouscron.be
robert.coulon@rhms.be
roland.devlieger@uz.kuleuven.ac.be
roland.van.dijck@hhleuven.be
simon.boes@pandora.be
sophie.perinatalite@gmail.com
sophie.servaes@skynet.be
steven.hellebaut@ziekenhuiswaregem.be
Thierry.decortis@chrcitadelle.be
tina.vanderheyden@obgyn.be
tomslangen@pandora.be
urbain.verboven@rzst.be
v.dallemagne@chdinant.be
vdepauw@scarlet.be
verhulst_guy@hotmail.com
victor.fonze@chh.be
voets.willy@skynet.be
waertsens@yahoo.com
walter.foulon@uzbrussel.be
wautersh@skynet.be
wilfried.gyselaers@zol.be
willem.ombelet@telenet.be
xdemuylder@clstjean.be
yolande.christiane@gmail.com
yves.jacquemyn@uza.be
Yvon.Englert@erasme.ulb.ac.be

To each participant it was asked whether they were answering this questionnaire as Head of MIC or his/her delegate, Head of NIC or his/her delegate, Head of Maternity without P* or his/her delegate, Head of Maternity with P* or his/her delegate, College Mother New Born member, Expert for College Mother New Born and/or representative of GGOLFB/VVOG scientific societies to the College (cumulative response possible).

<u>Time frame</u>

The first round took place on February 6th 2012. An official e-mail with link to the questionnaire was sent to all participants.
The introduction letter was :

> *The MIC (Maternal Intensive Care) beds are designed to allow intensive observation and care of patients whose pregnancy is at high risk, of women who require highly specialized care after delivery, or whose babies require intensive care after birth.*
> *Since 1996, 18 of the 106 Belgian maternity wards are equipped with MIC beds and a neonatal intensive care service. The number of MIC beds is independent of the size of the maternity and varies between 8 and 20 by maternity. In practice, MIC beds do not constitute a separate setting but are embedded in a maternity setting and are eligible for additional funding that strengthens the team of midwives specialized in the care of high risk pregnancy.*
> *The law has not detailed the indications for admission to a MIC bed. Therefore large variations exist between hospitals in terms of admission and referral policy. According to the*

KCE report of 2008, only 40% of patients with high-risk pregnancy are actually admitted to a MIC.

*Tools to determine the level and quality of MIC activity lack as well as tools to evaluate the operational functioning of the MIC centers in terms of meeting criteria for MIC admission, transfer and re-transfer. **That's why the College Mother and Newborn wishes to select indicators of quality of MIC with your help.***

The following questionnaire is the first round of a series of rounds of a Delphi survey. During the first round, we ask you to rate the importance of a set of potential quality indicators, which could be followed routinely to assess the quality of a MIC setting. Two dimensions of each potential indicator should be considered: its validity and its feasibility. If you wish, you can comment on the quality indicators in the dedicated areas. You can also add quality indicators that you consider necessary to assess and follow the quality of MIC.

You can now begin to answer the questions. To maximize the reliability and consistency of judgment, it is best to complete the questionnaire in one session.

Thank you very much for your collaboration.

After 2 weeks the response rate was merely 10%. Hence the MIC subgroup decided that each member would try to motivate collegues to respond. The enquete was sent around a second time on 13th March 2012. The first round was closed on June 30th 2012.

The second round was sent to all respondents of the first round on July 23th with a reminder on August 27th 2012.
The introduction letter was :

As you know, the College Mother-Newborn is actually working on the selection of tools able to determine the level and quality of MIC activity and the operational functioning of the MIC centers in terms of meeting criteria for MIC admission, transfer and re-transfer.

The College Mother-Newborn wishes to deeply thank you for your participation to the first round of this enquiry. Finally thanks to your commitment, the rate of respondents reached the expected level usually observed with a methodology using e-mail.

Thank you for your support to the College Mother-Newborn showing how it remains a credible and living dialogue platform between obstetricians and the Health Authority.

Following the first round, the questionnaire is now submitted to your evaluation for a second time and is addressed only to those who answered to the first solicitation. Some criteria have already been discarded due to a very low mean value observed after your first evaluation (average less than 2 on the validity scale) or some others which had reached a very high value (average more than 4 on the validity scale) have already been selected as valid tools. We have also taking into account your comments and proposals concerning other tools that could be useful.

We wish to remind you that the elected criteria in this inquiry should be followed routinely to assess the quality of a MIC setting (feasibility) and should reflect the efficacy and the quality of the functioning of the MIC (validity).

During the second round, we ask you to look at the average value obtained after the first round. This iterative approach allows you to reconsider your judgements in the light of feedback from peers. This process also gives you more time to think before committing yourself, leading to a better quality of response.

Finally we remind you that the anonymity of the approach enables all of us to express our opinions freely, without institutional loyalties or peer group pressures getting in the way.

You can now begin to answer the questions. Please do complete the questionnaire in one session.

Thank you very much for your collaboration.

3. Results

Response rate

The response rate in first round was 45,3% (58/128) which is the expected level for an inquiry performed through internet contact.

Participants first round	(n = 58)	
Head of MIC	27.6%	(16/58)
Head of NIC	22.4%	(13/58)
Head of maternity without P*	20.7%	(12/58)
Head of maternity with P*	24.1%	(14/58)
No answer	5.8%	(3/58)

Participants first round	(n= 58)
College Mother Newborn Member	27.6%
Expert for College Mother Newborn	15.5%
Representative of GGOLFB/VVOG	32.8%
None of them	24.1%

88,9% of the heads of MIC, 68,2% of heads of NIC participated. Obstetricians involved in the scientific society and in the College activities were strongly active in the process inquiry. Most of the non-participants were heads of maternity.

The response rate in second round was 70,6% (41/58)

Participants second round	(n = 41)	
Head of MIC	24,4%	(/41)
Head of NIC	24,4%	(/41)
Head of maternity without P*	19,5%	(/41)
Head of maternity with P*	21,9%	(/41)
No answer	9,8%	(/41)

Participants second round	(n= 41)
College Mother Newborn Member	21,9%

Expert for College Mother Newborn	**19,5%**
Representative of GGOLFB/VVOG	**29,3%**
None of them	**29,3%**

<u>List of valid and feasible indicators</u>

Out of the list of indicators, the following were judged as valid AND feasible:

Related to STRUCTURE

-**Neonatal Intensive Care Unit in same hospital**
-**Intensive Care Unit in same hospital**
-**Operating Room in labor ward**
-**Interventional radiology in same hospital**
-**Blood bank in same hospital**
-**24h/24h availability of trained midwives in MIC**
-**24h/24h availability of competent MIC OB/GYN (on call)**
-**24h/24h availability of anesthesiologists in hospital**
-**24h/24h availability of surgical team to handle all major obstetrical complications**
-**24h/24h availability of neonatologists**
-**Capacity to perform 3th level Ultrasound**
-**Capacity to do Invasive Prenatal Diagnostics**

Related to PROCEDURE

-**Multidisciplinary staff meeting weekly**
-**Availability of locally adapted guidelines**
-**Availability of locally adapted guidelines to the referring centers**
-**Regular contact between referring and referral centers for a specific patient by phone**
-**Access to written charter of admission criteria for MIC**

Related to OUTCOME

-**Permanent education of medical staff**
-**Permanent education of midwifery staff**
-**Number of intrauterine transfers (IUT) to P* function per year**
-**Number of admissions of MIC patients per year**
-**Number of MIC patients per year**
-**Number of births < 28 weeks per year**
-**Number of births < 32 weeks per year**
-**Number of babies with birth weight < 1000 g per year**
-**Number of babies with birth weight < 1500 g**
-**Number of babies > 22 weeks with congenital abnomalities who need Neonatal Intensive Care and/or surgery per year**
-**Number of severe Obstetrical Complications or 'near-miss' events (eclampsia, uterine rupture, peripartum hysterectomie or embolisation of uterine vessels) per year**
-**Number of Preeclampsia/HELLP/acute fatty liver of pregnancy < 34 weeks per year**
-**Number of deliveries of severely ill mothers (severe astma, liver failure, renal failure, severe heart disease, sickle cell anemia...) per year**

4. Conclusion

The MIC subgroup identified a list of indicators, judged as valid and feasible, that could be used to assess the quality of a MIC.
One of the main problems is that there is no definition of a MIC patient nor of admission criteria for MIC. Hence indicators as 'number of MIC patients per year' are still subject to huge bias, depending on the local organization of MIC and Maternity.

Nevertheless, the MIC subgroup deemed that the list of quality indicators might be useful for local data bases, hospital managers, national data bases and policy makers.

Registry and surveillance of rare complications in pregnancy

General Introduction

Following the initiative by the European Commission and the European Medicines Agencies (EMEA) to encourage the research, the development and the marketing of "orphan" medicines to treat, prevent or diagnose rare diseases, the European Commision sent a note to the European Parliament, to the Council and to European economic and social committee as well as the committee of the regions on the problem of "rare diseases".

Rare diseases are defined by the European Union as diseases with a prevalence of 5 or less per 10 000 persons. The European Commission considers that *"The lack of specific health policies for rare diseases and the scarcity of the expertise, translate into delayed diagnosis and difficult access to care. This results in additional physical, psychological and intellectual impairments, inadequate or even harmful treatments and loss of confidence in the health care system, despite the fact that some rare diseases are compatible with a normal life if diagnosed on time and properly managed. Misdiagnosis and non-diagnosis are the main hurdles to improving life quality for thousands of rare disease patients."*

What is being said on rare diseases in general is also true for pregnancies of the mother to be with a rare disease or a rare complication of pregnancy, herewith not only risking the life of the mother herself but also that of the child to be born

Registries and databases constitute key instruments to increase knowledge on rare diseases. Indeed, the use of registries and databases are excellent means for pooling information in order to achieve a sufficient sample size for epidemiological as well as clinical research. Such an approach will indeed **improve the health** care as has been demonstrated by Larsson and his colleagues using 13 disease registries in 5 different countries (Larsson et al 2012 The lancet) .

Objective

The purpose of present study protocol is to achieve **a registry and a surveillance** of rare complications of pregnancy in Belgium.
Some complications in pregnancy are so rare that few midwives and obstetricians will ever in their whole careers come across them.The purpose of creating a registry and a surveillance for those rare complications in pregnancy is to bring together expertise on the knowledge and the management of those conditions so that in future pregnant women with a rare complication of pregnancy could benefit through better information on the condition and the outcome of the condition. By pooling those rare cases together it becomes possible to study the best possible management because at present the clinical practice is rarely based on robust evidence.

A similar initiative was taken in the U.K. already in 2005 under the impulse of Dr Marian Knight and is called the "UKOSS, United Kingdom Obstetrics Surveillance System, project".

She and a team of experts is working together with the RCOG, the Royal College of Obstetricians and Gynaecologists, in London and with the NPEU, the National Perinatal Epidemiology Unit, in Oxford. The methodology they used was that developed by the BPSU to study rare disorders in childhood.

The Doctors of the college for 'the Mother and the Newborn' have suggested a similar approach in Belgium and have decided to start by investigating the following three complications 1) eclampsia 2) uterine rupture 3) postpartum hysterectomy and/or embolization of the uterine arteries.

Definitions of the selected topics were set as follows:

Eclampsia defined according to UKOSS as any woman with **convulsion(s)** during pregnancy or within the first 10 days after delivery, in combination with at least 2 of the following features within 24 hours of the convulsion(s) :

- **Hypertension** : a maximum diastolic Blood Pressure of >= 90 mmHg and a diastolic increment of >= 25 mmHg (having had a diastolic Blood Pressure <90 mmHg at the first antenatal visit)
- **Proteinuria** : at least + protein in a random urine sample or >= 0.3 g of proteins in a 24-hour collection
- **Thrombocytopenia** : platelet count < 100000/ml
- **Raised transaminase levels** : ALT of >= 42 IU/l or AST of >= 42 IU/l

For Uterine rupture a larger definition is used including all uterine rupture cases as defined by UKOSS, but also to consider all other forms of uterine rupture as defined by the LEMMoN study in the Netherlands.

Uterine rupture as defined by UKOSS (a complete separation of the wall of the pregnant uterus, with or without expulsion of the fetus, involving rupture of the membranes at the site of the uterine rupture or extension into uterine muscle separate from any previous scar, and endangering the life of the mother or the fetus),

Uterine rupture as defined by the LEMMoN study in the Netherlands (the occurrence of clinical symptoms (abdominal pain, abnormal fetal heart rate pattern, acute loss of contractions, vaginal blood loss), leading to an emergency caesarean delivery, at which the presumed diagnosis of uterine rupture was confirmed; or peripartum hysterectomy of laparotomy for uterine rupture after vaginal birth

UKOSS and LEMMoN both excluded any asymptomatic palpable or visualized defect (for example dehiscence) noted incidentally at caesarean delivery.

Postpartum Hysterectomy and embolisation of the uterine arteries as defined by UKOSS: being any woman giving birth to a fetus or infant and undergoing a **hysterectomy** in the same clinical episode. Similarly "peripartum embolization of the uterine arteries" will be considered when occurring in the same clinical episode.

Methodology

The methodology used is based on UKOSS, which in turn is similar to the methodology developed by the BPSU, British Paediatric Surveillance Unit, which was in 1986 to undertake active surveillance of rare paediatric disorders.

It concerns anonymous descriptive cohort studies through a monthly case-collection scheme. Each hospital with a maternity unit has been asked to participate through either an obstetrician or a midwife to report to B.OSS. Every month, every unit is sent a "rapporteringsformulier" with a list of the 3 conditions under surveillance (see below attachment 01 the Dutch version of the form). They are asked to tick the boxes indicating if any cases have occurred in the previous month, or if none, to return the card indicating a nil return. If there is no reply, consecutive reminders are being sent.

On receiving a case report (return of the monthly forms), the B.OSS team will dispatch a data collection form or questionnaire to receive more detailed information about the case. The data collection forms have been developed individually for each condition in a way that the information obtained allows comparison with the UKOSS and the LEMMON data from the United Kingdom, and the Netherlands. Help with the completion of the form is being offered. A hospital case note number is requested for in case further information is required. No personally identifiable information is kept in the analysis of the data. Patients concerned are all informed of the study and they can refuse participation by opting out (see attachment 02 – information leaflet for the patient the Dutch version of the leaflet)

Short overview of the course of the project since July 2011

The Belgian Obstetric Surveillance System, briefly called "B.OSS", has been constituted and an appropriate logo has been created.

B.OSS **is conducted by two teams**: one team for the Dutch-speaking maternities in Flanders and the VUB in Brussels and one team for the French and German-speaking maternities in Wallonie and Brussels with the exception of the VUB in Jette. The teams cooperate and meet every three months to update on their progress, to discuss difficulties and help finding solutions, to propose ideas for further improvement. All the correspondence between the B.OSS team and the gynaecologists/midwives/maternities is done either *in the Dutch* or *in the French language*.

Extensive d**ata collection forms (one for each complication under consideration)** have been developed *in the English language*. The forms have been based on the UKOSS data collection forms, with adaptations and additions based on similar international studies on the topic, to enable comparison of the data with other countries including the LEMMoN study in the Netherlands. The data collection forms seek confirmation of the appropriate case definition and additional information on risk factors, management and outcomes.

The collection of patient information by B.OSS has been **formally approved by the Medical Ethics Committee** of the University Hospital Ghent (EC UZG 2012/734; B670201215359) and by the Medical Ethics Committee of the University Hospital Brussels (EC ULB 2012/111; B406201213660) provided an information letter will be offered to the patient, enabling an opt-out system. See attachment 02 at the end of this document, showing the letter of information for the patient involved and enabling an opt-out system – the attachment gives the letter in the Dutch language, yet the same letter also exists in the French language.

Besides the financial support from the College of Mother and Child, approval and endorsement for B.OSS has been requested and obtained from the VVOG (VWV, Vlaamse werkgroep Verloskunde), GGOLFB, SPE and CEpiP, the various universities and the perinatal Centres in the country.

August – December 2011: **One or more gynaecologists including the head of unit of each maternity hospital in Belgium have been contacted** by telephone and/or by e-mail, and they were informed about the B.OSS: the background, aims and procedure. They were asked firstly, **if they agreed to participate** in the B.OSS project, and secondly**, if they could nominate a dedicated contact-person** who should be responsible to report to B.OSS. A contact person was sought for every group of gynaecologists. This contact-person could be a gynaecologist or a midwife. Special attention has been given to maternity hospitals consisting of several teams of associated gynaecologists and gynaecologists who operate individually.

From January 2012 onwards: all contact-persons have been sent **a 'case reporting form'** (see above and the attachment 01) on which they find four tick boxes: one for each of the three obstetric disorders under surveillance and one indicating none of the three disorders has occurred. They are asked to complete and return the reporting form, emphasizing the importance of returning the form even if no case has occurred in the previous month.
The Dutch-speaking team has registred retrospectively for October, November and December 2011. The 'calls for registration' that followed were 2-monthly (January 2012, March 2012, May 2012) and occurred monthly since June 2012. The French-speaking team has sent monthly 'calls for registration' since February 2012 to report from January 2012.

When a case is reported on this monthly mailing, the B.OSS team is sending **a 'data collection form'** to the reporting contact-person and/or the gynaecologist responsible for the case, to collect more detailed information about the case. They are free to fill out the data collection form themselves independently or they can ask for a B.OSS team member to come at the spot to fill in the form together.

The B.OSS data collection forms do not collect any personally identifiable information, such as names and addresses, except for the year of birth and/or hospital number to facilitate communication and retrieval of further information if required to clarify the case Returned data collection forms are checked for completeness by the B.OSS-team. When data are missing or unclear the reporting gynaecologist is contacted for further information.

Results as to 31/12/12

We count 104 Belgian maternity hospitals, some of them existing of two or more campuses or associations that register separately making a total of 115 Belgian centres that are considered for registration. **97,3 %** (112/115) of the Belgian centres agreed with the principles. Two centres declined participation and one centre has never replied on several attempts to contact. All participating centres except 4 have responded at least once at the monthly call for cases: hence **93,9 %** (108/115) of the Belgian centres is actually particating .
We count 104 Belgian maternity hospitals, some of them existing of two or more campuses or associations that registrate separately making a total of 115 Belgian registrating 'centers'.
97,3 % (112/115) of the Belgian centers is participating in B.OSS. Two centers declined participation and one center has never replied on several attempts to contact them.
All participating centers except 4 have respondedat least once at the monthly call for cases:
93,9 % (108/115) of Belgian centers is registring.
The response rate from January 2012 until December 2012 was **90 %** (1210/1344). The table underneath illustrates the monthly response rate in 2012.
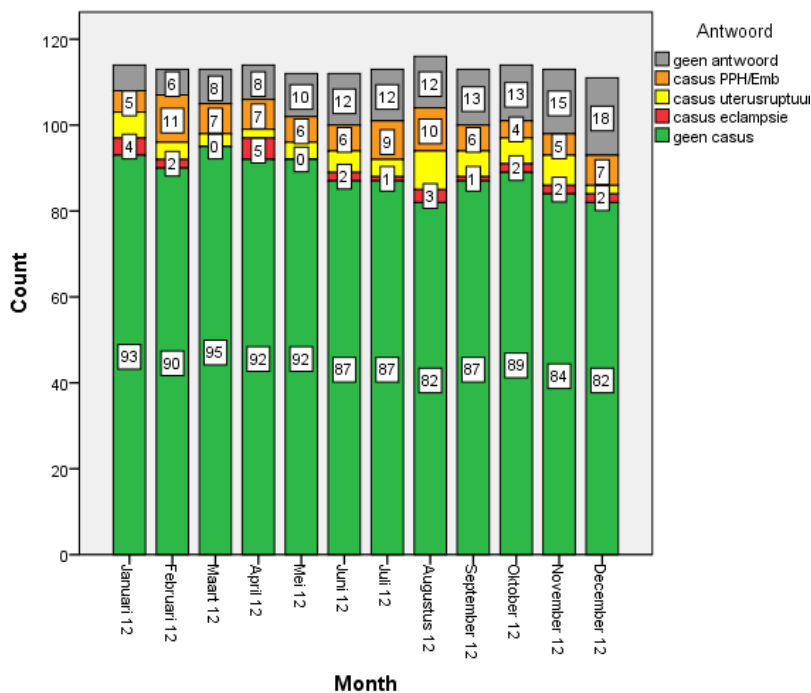
To improve the response rate frequent reminders have been sent when there was a delay in returning the monthly reporting form or the data collection form. Reminders have been sent by e-mail or by contacting the reporting gynaecologist by telephone.

In 2012 the number of **cases of each of the three topics reported** were as follows:
- **25** cases of Eclampsia: incidence of 1.9 / 10 000 deliveries
  (using an estimated 129 000 deliveries in Belgium in 2012 as denominator)
- **55** cases of Uterine Rupture: incidence of 4.2 / 10 000 deliveries
- **80** cases of Postpartum hysterectomie and/or embolization: incidence of 6.2 / 10 000 deliveries

The number of **data collection forms** that have been **completed** and returned is 23 (after 1 exclusion of 1 case not considered to be an eclamptic episode) on Eclampsia, 46 on Uterine Rupture and 59 on Postpartum hysterectomy and/or embolization.

All reporting contact-persons and maternity hospitals have been informed of the current state with **a newsletter,** the first newsletter was sent in November 2012 reporting on the number of participating hospitals, the accurateness of reporting, the number of reported cases and the number of completed data collection forms. From the LEMMoN study we learn that completeness of data collection is no easy task.

The second newsletter has been sent in February 2013.

Contacts are kept with the participating centres by Newsletters (in Dutch for the Dutch-speaking centres and in French for the French and German speaking centres)

A first newsletter in November 2012 reported on the number of participating hospitals, the accurateness of reporting, the number of reported cases and the number of completed data collection forms.
A second newsletter has been sent in February 2013
A third newsletter is ready to be sent by the end of June 2013 – we are awaiting for the München-meeting (= INOSS meeting) to report upon in that newsletter;

Reports – so far reports were discussed internally and with the College Mother & Child

The data that has been collected until December 31, 2013 will be analysed between January and June 2014

The formation of B.OSS (part of the College Mother and child) and its first results have been **presented on several occasions at national and at international meetings as listed below:**

1- **VVOG – Postuniversitaire studiedag, mei 2012**
2- **ISOM, the International Society of Obstetric Medicine – Oxford - 6th international meeting in July 2012**
3- **INOSS, the International Network of Obstetric Survey Systems – Paris 2012**
4- **VVOG – Assistentendag, maart 2012**
5- **Den Doelen Congres, Rotterdam the Netherlands in april 2013**
6- **ISSHP – Tromso, Norway June 2013**
7- **INOSS – Münster, GrmanyJune 2013**

Meanwhile, in view of the pitfalls encountered, the data collection forms have been revised and the idea of creating a website for web based data collection and feedback information to all participants (= all healthcare workers involved in obstetrics) has evolved.
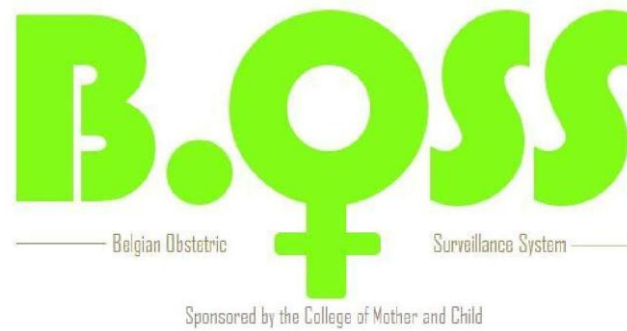
RAPPORTERINGSFORMULIER

Zeldzame verwikkelingen van de zwangerschap.

Gelieve dit formulier binnen de week terug te sturen naar B.OSSVlaanderen@gmail.com

GELIEVE PER CASUS een kaart terug te sturen – waarvoor dank --

Verloskundig CENTRUM

NAAM contactpersoon

EVALUATIE gedurende de maand _____ jaar _____

☐ GEEN ENKELE COMPLICATIE in DEZE MAAND

☐ Eclampsie

☐ Uterusruptuur

☐ Peripartum hysterectomie of embolisatie van de Aa. Uterinae

Bij twijfel of de casus in aanmerking komt, adviseren we steeds wel aan te melden, om onderrapportering te vermijden.

Lokaal dossiernummer :

CONTACTGEGEVENS ingeval van rapportering van een casus:

Naam contactpersoon

Te bereiken via E-mail

Te bereiken via telefoon

Bij voorkeur contacteren op

Bij voorkeur niet contacteren op

Hartelijk dank voor uw medewerking.

Attachment 02 informatie brief voor de patiente en/of familie Nederlandstalige versie

<div style="border:1px solid black">

Belgian Obstetric Surveillance System (B.OSS)

Studie naar ernstige zeldzame verwikkelingen van de zwangerschap en bevalling

In opdracht van en gefinancierd door het College van Moeder en Pasgeborene
(F.O.D. Volksgezondheid, Veiligheid van de voedselketen en Leefmilieu)

</div>

Informatiebrief bedoeld voor de patiënte of een familielid dat fungeert als haar wettelijke vertegenwoordiger.

Geachte Mevrouw,

U heeft recent tijdens uw zwangerschap en bevalling een ernstige complicatie doorgemaakt.
Dit is een complicatie die slechts af en toe voorkomt en daardoor nog maar weinig is onderzocht.
Graag willen we onze kennis over dit soort complicaties verruimen, en zo mogelijk onze kwaliteit van zorg verbeteren. Dit willen we doen in een studie die bovenvermelde titel/naam draagt..

Hiervoor zouden we bepaalde gegevens uit uw medisch dossier verzamelen in een databestand, zodat we deze kunnen bundelen met gegevens van andere patiënten die een zelfde complicatie hebben doorgemaakt.
De gegevens die verzameld worden zijn vertrouwelijk en uw anonimiteit is gewaarborgd.
Ook zal dit verzamelen van gegevens niets veranderen aan uw opname, de behandeling die u krijgt of de relatie met uw gynaecoloog of verzorgend team.

U bent niet verplicht om aan deze studie deel te nemen. Indien u dit niet wenst, kunt u dit steeds aan uw gynaecoloog laten weten. Als u geen bezwaar aangeeft, zullen we de relevante gegevens uit uw medisch dossier opnemen in de studie.

Een gelijkaardig e studie loopt reeds in meerdere landen. Hetzelfde gebeurt in het Franstalig landsgedeelte en de gegevens uit Vlaanderen en uit Wallonie en Brussel zullen samen worden verwerkt. Deze studie werd meer specifiek geëvalueerd en goedgekeurd door het ethisch comité van het Erasmus Ziekenhuis (ULB) in Brussel en van het UZ Gent.

Alvast hartelijk dank,

Het B.OSS- onderzoeksteam.
Prof. Dr. Myriam Hanssens, KUL, UZ Gasthuisberg Leuven
Prof. Dr. Yvon Englert, ULB, Hôpital Erasme and CEpiP
Dr. Griet Vandenberghe, UZ Gent
Dr. Joachim Vankeirsbilck, Sint Jansziekenhuis Brugge
Dr. Marine Guisset, UZ Gasthuisberg Leuven
Dr. Marlies Deblaere, UZ Gent
Mevr. Virginie Van Leeuw, CEpiP
Mevr. Ann Langedock, laatste jaarstudent Geneeskunde KU Leuven

National register for epidemiological record, concerted management related to rare gestational trophoblastic diseases.

BACKGROUND

Gestational trophoblastic diseases represent a large spectrum of heterogen and rare conditions. They are characterized by abnormal placental growth and development leading to aborted pregnancy. Recently, in order to harmonize the nomenclature, a simplify classification was proposed by the WHO (Genest et al., 2003). It distinguishes premalignant tumors (complete and partial hydatidiform moles), invasive diseases (invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor (ETT)) and benign conditions as placental site nodule and exaggerated implantation site. These diseases are characterized by hyperplasic trophoblast inducing human chorionic gonadotrophin (hCG) hypersecretion (Philippe et al., 1998).

Complete mole occurs in 1/1000 pregnancies while partial mole happens on 3/1000 pregnancies in Europe. The gestational trophoblastic neoplasia are even less frequent (1/40 000 pregnancies for choriocharcinoma) (Jacobs et al., 1989, Lee et al., 2009).

Due to their low occurrence and heterogeneity, the diagnosis, follow-up and treatment are often not optimal. However, each step is essential for appropriate management, in order to avoid under or over treatment.

Diagnostic difficulties have been demonstrated by different studies. Partial moles are reviewed in complete moles in 25% of cases. No gestational disease are concluded in 23,2% and do not require any treatment or specific follow-up (Paradinas 1998, Paradinas et al., 1996). This is confirmed by another study, where 28% of partial moles are found to be complete moles and 7% are non-molar pregnancies. Moreover, 7% of initially diagnosed choriocarcinoma are reviewed in PSTT or ETT involving a specific treatment (Golfier et al., 2011).

Incomplete follow-ups have also been reported. Even while the molar pregnancy follow-up seems easy consisting in close hCG monitoring, weekly until negativation and thereafter monthly for a period of 6 months, these apparently "easy guidelines" are not followed in about 30% of cases (Feltmate et al., 2003; Bartofi et al., 2004).

Treatment mistakes are also observed. French Centre has shown that 34% of patients have been inadequately treated, either they did not require any treatment, either they have been over- or under- treated (8, 7% and 10 % respectively) (Golfier et al., 2007).

These different weaknesses of gestational trophoblastic disease management could be overcome by systematic referring to expert centre.

Strict adherence to such a systematic policy has even been shown to translate in a significant decrease in the rate of fatal cases of GTN Lybol 2012, BJOG, Fatal cases of GTN over four decades in the Netherlands : a retrospective cohort study)

Based on the experience from different European countries (UK, Netherlands, France, Switzerland, …), we set up a Belgian national register system inspired by our European predecessors, combined with two reference centres (IEC/IRB approved) created to help physicians and their patients.

In parallel, a website was generated (www.mole-chorio-bgog.eu) containing information for patient and physician, including registering form and informed consent. First data are presented below.

This initiative was presented and supported by our national professional societies, GGOLFB (Groupement des Gynécologues-Obstétriciens de Langue Française en Belgique) and VVOG (Vlaams

Vereniging voor Obstetrie en Gynaecologie) and the database was created thanks to the BGOG (Belgian Gynecologic Oncology Group).

MATERIALS AND METHODS

I. REFERENCE CENTRES: RULES OF FUNCTIONING

Once a physician discovers a molar pregnancy, he contacts the centre via phone or by sending directly documents found on the website. First guidelines are given based on initial pathology report, awaiting the review by expert panel. The pathologist's expert panel for French part is composed of pathologists from ULg (Pr P. Delvenne and Dr K. Delbecque), ULB (Pr JC Noel), and UCL (Pr E. Marbaix). Pr P. Moerman (KUL) is the reviewing expert pathologist for the Flemish part. The reviewed diagnosis is then communicated to initial pathologist and referring physician. In the mean time, the data manager collects weekly hCG values to establish a follow-up chart based on Schlaerth's curve (see Figure 1).
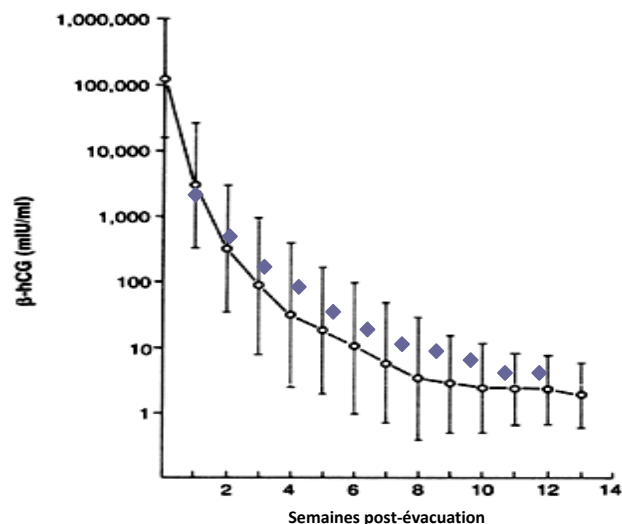

Figure 1: Example of hCG regression curve (logarithmic scale) in case of complete mole follow-up. Blue dots represent real values of hCG plotted on a standard regression curve established by Schlaerth et al (1981).

The physician is regularly informed by mail of hCG evolution. Letters are sent at inclusion, at pathology revision, at hCG negativation, and at the end of hCG follow-up.
In case of abnormal hCG evolution (raise, plateauing or positivity at 6 months,) or if a neoplasia is anatomopathologically diagnosed (choriocarcinoma, PSTT or ETT), physician is immediately contacted by phone by referent gynaecologist. A complete work up including pelvic US with Doppler, pelvic RMN, thoraco-abdominal CT-scan with chest radiography if pulmonary nodules are present and brain RMN, is planned to determine the adequate treatment.
Based on imaging results, FIGO stade and score are calculated to determine the risk. In case of low-risk, a monochemoterapy is settled, while a polychemotherapy is started in case of high-risk disease.
The rules of functioning have been sum up in the Editorial of Gunaikeia (Goffin and Vergote, 2011).

II. DATABASE

Besides the reference centres, one unique national secured web-based database has been created and hosted on BGOG server.
Data managers from both centres encode new cases on a regularly base.
Extraction can be done to Excel sheet to allow statistical analysis.

The database has been created taking into account the already existing databases from Charing Cross centre (Pr Seckl and Mitchell), the French Registry in Lyon (Pr Golfier) and the Swiss Centre in Geneva (Pr Petignat).

The following items (more than 200 items) have been considered among these different topics:

- Demographics;
- Obstetrical history;
- Index pregnancy;
- Initial and reviewed pathology;
- Imaging work-up;
- Proposed and followed treatments;
- hCG follow-up;
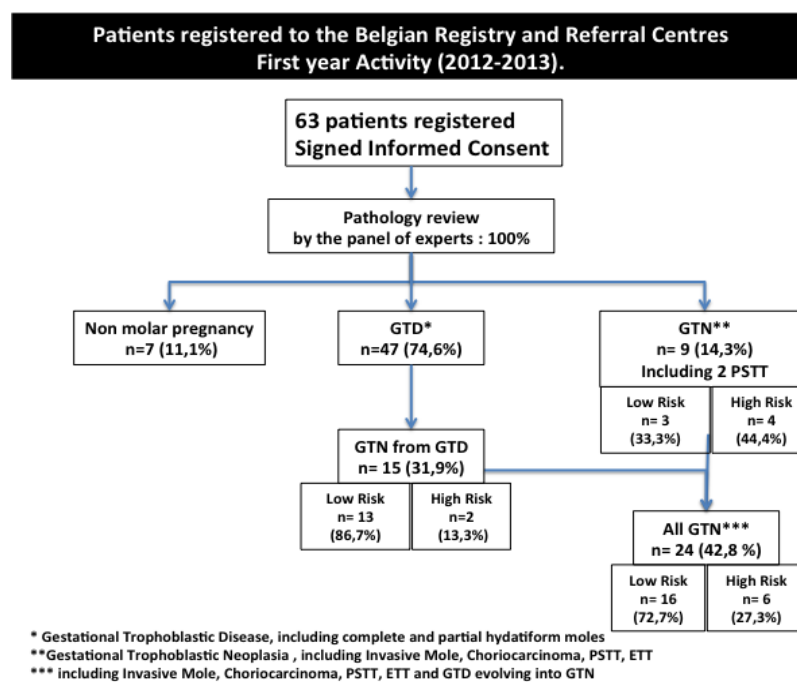- Disease evolution.

RESULTS

Figure 2: Repartition of patients registered to Belgian Registry between July 2012 and March 2013, adapted from Golfier et al., 2007.

The Belgian national register and reference centres were officially opened for accrual in July 2012. From July 2012 to March 2013, 63 patients with presumed GTD or GTN were registered at the Belgian Registry for GTD after receiving signed Informed Consent Form (Figure 2). Thirty-seven and 26 patients were registered through the French and the Flemish centres, respectively. The map (Figure 3) represents the geographic distribution of the registered cases.

Median age at diagnosis is 32 years old (range 18-53) and 19% are older than 45 years old. The majority of women are White/Caucasian (79%), 14,6% are North African, and 4,2 % are Black African.

Figure 3: Geographic repartition of cases registered to Belgian Centres.

I. HISTOLOGICAL REVIEW

	Reviewed pathology (n=63)						
	Abortion	PM	CM	Invasive mole	CC	PSTT	ETT
Initial Diagnosis (n=63)							
Abortion n=2 (1/1)					1 (0/1) (50%)		1 (1/0) (50%)
PM n=27 (9/18)	6 (0/6) (22%)	14(8/6) (52%)	7(1/6) (26%)				
CM n=29 (14/15)	1 (0/1) (3,5%)	1 (0/1) (3,5%)	25 (13/12) (86%)	2 (1/1) (7%)			
CC n=4 (2/2)					3 (2/1) (75%)	1(0/1) (25%)	
PSTT n=1 (0/1)						1(0/1) (100%)	

Table 1: Comparison between initial pathology and reviewed pathology.
Numbers under brackets correspond to Flemish / French centres.

The distribution of presumed diagnosis compared to reviewed pathologies by the expert panel is described in the Table 1. Between July 2012 and March 2013, the referent pathologist's panel of expert reviewed the histological slides of all patients referred. The overall rate of agreement with the referring centre was 68 % (43 of 63). When the initial diagnosis was complete mole (CM), we found a 86 % rate of agreement (25 of 29); in the 4 cases of disagreement, patients were reclassified as abortion (n=1), partial mole (PM) (n=1) or invasive mole (n=2). When the initial diagnosis was PM, we found a 52 % rate of agreement (14 of 27); about 22% of disagreements (6 of 27) were reclassified as nonmolar pregnancies and 26 % (7 of 27) as CM.

1. Final pathology "down graded" the final diagnosis for 8 patients as follows :
   a. 7 presumed moles (6 PM and 1 CM) have been reviewed in miscarriage,

b. 1 supposed CM is reviewed in PM,

  Follow up is not needed and patients can consider a new pregnancy without delay.

2. Final pathology "up graded" the final diagnosis for 12 patients :
  a. 1 case of miscarriage was corrected to CC after bad evolution of hCG and review of the case,
  b. 7 patients who developed supposed PM had CM
  c. 2 patient with supposed CM had a IM
  d. 1 patient with miscarriage was corrected to ETT
  e. 1 patient with supposed CC was reviewed into PSTT

  Due to pathology review, those patients benefit from accurate treatment with chemotherapy and/or hysterectomy for 3 of them (1 CC treated by chemotherapy, and 1 ETT and 1 PSTT who undergone hysterectomy and chemotherapy).

II.   MOLAR PREGNANCIES

Overall, 56 assumed molar pregnancies have been registered to the centre. Seven were reclassified as nonmolar pregnancies and two as invasive moles. Forty-seven patients were therefore considered for analysis: 32 were CM, 15 PM. The mean age of patients was 32 (17-53) years with a median 1.0 previous gestation (0-9).
GTN diagnosed with FIGO 2000 criteria developed in 15 of 47 patients with molar pregnancies (31,9 %), all developed from a CM.

III.   GESTATIONAL TROPHOBLASTIC NEOPLASIA

Twenty-four patients with GTN were analyzed. Among them, 9 (14,3%) patients were registered at the time of GTN and 15 (31,9%) were registered patients with molar pregnancies who developed GTN during their follow-up. Among these 24 patients with GTN, 2 were placental site trophoblastic tumor, 1 was epithelioid trophoblastic tumor, 4 were histologically proven choriocarcinomas, and 2 were histologically established invasive moles.
It is known that 10 to 15% of moles evolve into neoplasia (Jacobs et al., 1998). The diagnosis of posthydatidiform mole trophoblastic neoplasia, made according to 2000 FIGO hCG criteria, concerns 15 (31,9 %) patients. It is higher than expected. These results are probably biased due to our recent activity. Centres are not contacted at the diagnosis but later, when hCG evolution is bad. To avoid this bias, we need to gather more data and to explain as much as possible the benefit of Centre registration.
According to the 2000 FIGO scoring system (and therefore excluding PSTTs), 16 of 22 patients (72,7%) were low risk, whereas the remaining 6 patients (27,3%) were high risk. Among the 4 histologically proven choriocarcinomas, 1 was low-risk and 3 were high-risk patients.

DISCUSSION

We report here the preliminary Belgian epidemiological data on trophoblastic disease. Following the example of the French Trophoblastic Disease Reference Centre in Lyon, France and the London Charing Cross Hospital, the Belgian registry and centres were created in 2012 in Liège and Leuven, Belgium, with the support of BGOG, GGOLFB and VVOG.

Our experience shows an encouraging coverage of the expected cases and a high referral rate, with more than 90 % of the expected cases being registered and referred during the first year of activity (2012-2013).

In contrast to the British situation in which patients have to go to the reference centre, the organization of the Belgian centres was based on the voluntary reporting of cases by physicians in charge of the patients.

The creation of the Internet address of the centre (www.mole-chorio-bgog.eu) is aimed to provide up-dated information to physicians, patients and also give patients the opportunity to share their experience in a free-access forum.

The systematic pathology reviewing system by the panel of experts confirms the difficulty of posing accurate diagnosis by non-experts pathologists. The rate of pathology reclassification is in excess of more than 30%, which is unexpectedly high. By itself, this observation justifies the prolongation of this registry and reference system.

We report a high satisfaction of the community physicians who recognize the benefits of these medical services.

KNOWLEDGE EXCHANGE

I.   Publications

1. DELCOMINETTE et al. Registre belge et centres de référence pour les maladies trophoblastiques gestationnelles, 2013, Rev Med Liège, Submitted.
2. GOFFIN F, VERGOTE I. Un registre et un centre de référence de maladie trophoblastique en Belgique : Pour qui ? Pourquoi ? Gunaïkeia, Editorial, Septembre 2011,**16** : 203
3. RAUW et al. Atypical recurrence of a placental site trophoblastic tumor four years after hysterectomy for benign condition: Case report and review of literature. Gynecologic Oncology Case Reports, 2013.

II.   Posters presented during National or International Meeting:

1. Registre belge et centre de reference des maladies trophoblastiques gestationnelles.
   a. Annual Meeting of the European Society of Gynecology, SEG-ESG, Brussels, Sept 2013
   b. 2nd Onco-GF meeting, Brussels, November 2012.
2. Boulay et al, Incidental choriocarcinoma developed in term placenta associated with In Utero Fetal Death, Annual Meeting of the European Society of Gynecology, SEG-ESG, Brussels, Sept 2013
3. Systematic review of Gestational Trophoblasic diseases by an expert panel of pathologists. Timmermans M., Delbecque K., Delvenne P., Marbaix E., Noël JC, Moerman P., Vergote I., Kridelka F., Nisolle M., Goffin F. 3rd Belgian Week of Pathology, Ghent, April 2012.

III.   Oral communications during Scientific or Medical Meeting

1. Journées Liégeoises de Gynécologie-Obstétrique, 23 March 2012
2. Verviers, CHPLT, 2012
3. Erasme Hospital, Université Libre de Bruxelles, June 2012
4. Biannual Meeting of the ONCO-GF, November 2012
5. Annual Meeting of BGOG, Diegem, November, 2012
6. GLEM, Namur, December 2012.
7. CHIREC, June 2013

8.   Charleroi, September 2013

IV.   <u>Meeting attendance</u>

- 3rd Meeting of EOTTD to be held in May 2014, Liège, Belgium.
- XVIIth World Congress on Gestational Trophoblastic Diseases, September 2013, Chicago, US.
- 2nd Meeting of EOTTD, June 2012, Geneva, Switzerland,
- XVIth World Congress on Gestational Trophoblastic Diseases, Budapest, Hungary, October 2011.
- 1st Meeting of European Organisation for Treatment of Trophoblastic Diseases (EOTTD), Lyon, France, 2010.

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4. Lee et al, 3rd edition GTD book, p 49-95

5. Paradinas FJ - The diagnosis and prognosis of molar pregnancy : The experience of the National referral centre in London. Int J Gynaecol Obstet, 1998, 60, S57-64.

6. Paradinas FJ, Browne P, Fisher RA et al. - A clinical, histopathological and flow cytometric study of 149 complete moles, 146 partial moles and 107 non-molar hydropic abortions. Histopathology, 1996, 28, 101-110.

7. Golfier F, Clerc J, Hajri T et al. – Contribution of referent pathologists to the quality of trophoblastic diseases diagnosis. Hum Reprod, 2011, 26, 2651-2657.

8. Golfier F et al First epidemiological data from the French Trophoblastic Disease Reference Center, Am J Obstet Gynecol 2007.

9. Feltmate CM, Nartofi J, Fulop V et al. – Human Chorionic Gonadotropin Follow-up in patients with molar pregnancy: a time for reevaluation. Obstet Gynecol, 2003, **101**, 732-736.

10. Bartofi J, Vegh G, Szepesi J et al. – How long should patients be followed after molar pregnancy ? Analysis of serum hCG follow-up data. <u>Eur J Obstet Gynecol Reprod Biol</u>, 2004, **112**, 95-97

11. Golfier F, Labrousse C, Frappart L et al. – Evaluation de la prise en charge des tumeurs trophoblastiques gestationnelles enregistrées au Centre de référence des maladies trophoblastiques de Lyon de 1999 à 2005. Gynecol Obstet Fertil., 2007, 32, 205-215

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13. Goffin F, Vergote I. Un registre et un centre de référence de maladie trophoblastique en Belgique : Pour qui ? Pourquoi ? Gunaïkeia, Septembre 2011, **16** : 203