The clinical dilemma of treating breast cancer in pregnancy

Choices, risk and searching for answers

Philip Banfield MBBS MD DA PGCPCE FAcadMEd FRCOG

Acknowledgements

Claudia Hardy – Senior Clinical Research Fellow

Julie Jones - Associate Specialist, Oncology

Marian Knight - Professor of Maternal and Child Population Health, NPEU

- These are part of the UKOSS study team in north Wales

Aled Pleming - Consultant Obstetrician

Glynwen Lewis - Community Midwife

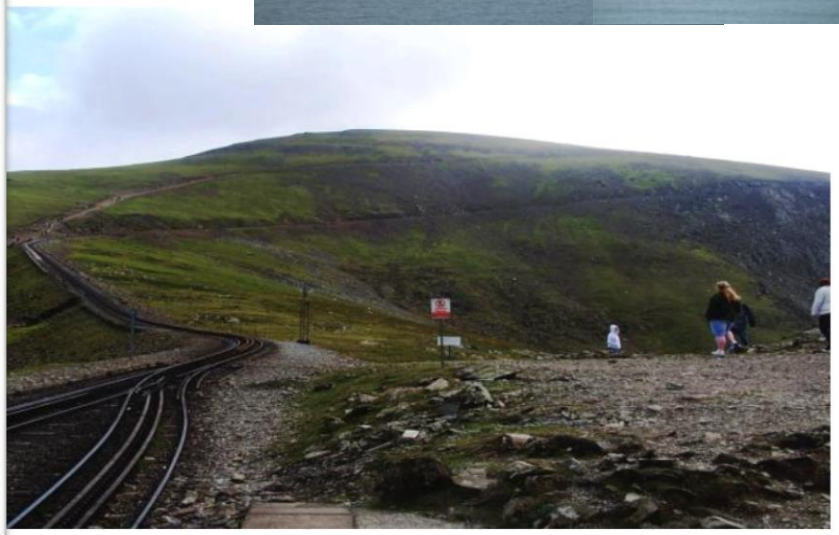
Cath Bale - Consultant Oncologist

Jill Bishop - Consultant Oncologist

Paul Cool - Consultant Orthopaedic & oncological surgeon, Oswestry

Claire Fuller - Specialty Doctor, Oncology

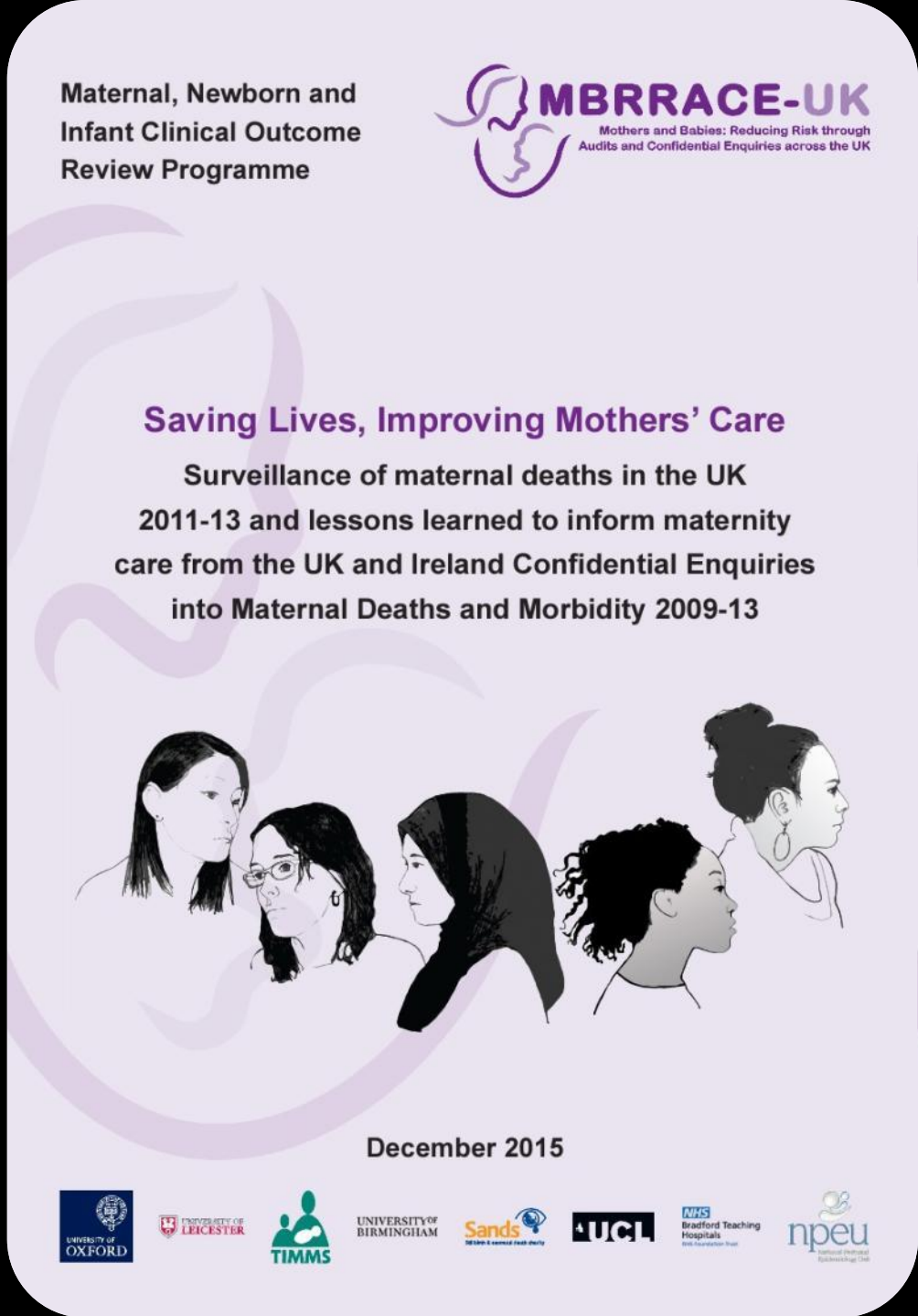
- These are part of the local MDT involved in the care of the case discussed



Welcome to north Wales

Because cancer in pregnancy is rare, many obstetricians find out about cancer through the confidential enquiries into maternal death, where the notes of each case (and reports from the clinical teams involved) are anonymised and each case is assessed by a panel of experts to look for lessons that can be learned to help the management of other women in the future.

Typically, in about 20-30% of cases, something is identified that may have made a significant difference to outcome if a different course of action had been taken, based on known standards, advice or guidelines.



Classification of care received by women who died as a result of malignancy 2009-13

	Total (n=64) Number (%)
Classification of care received	
Good care	30 (47)
Improvements to care which would have made no difference to outcome	17 (27)
Improvements to care which may have made a difference to outcome	3 (5)
Insufficient information to classify	14 (22)

Slide courtesy of MBRRACE

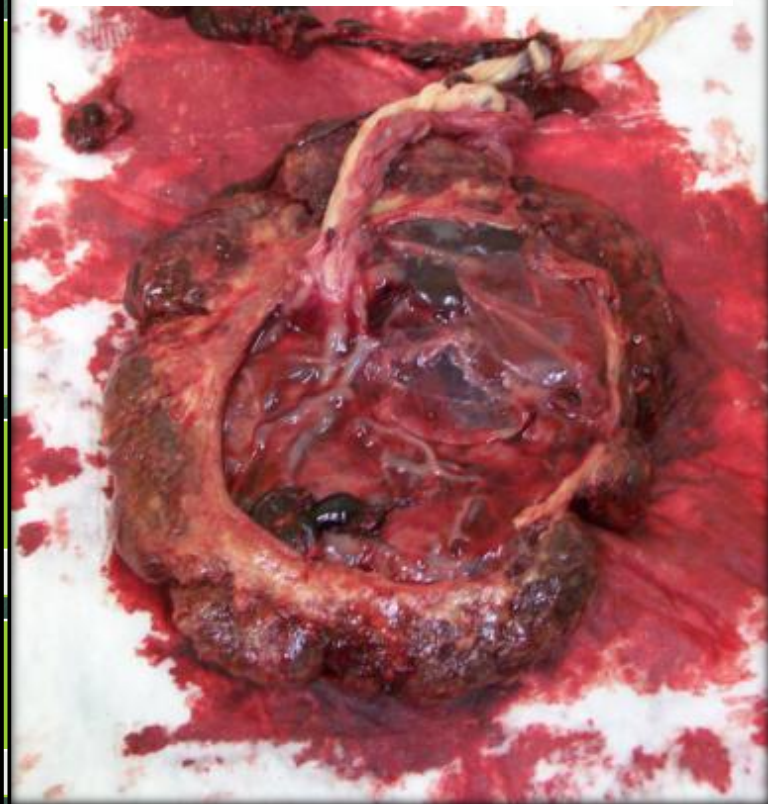
MBRRACE-UK
Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

Confidential enquiry advice

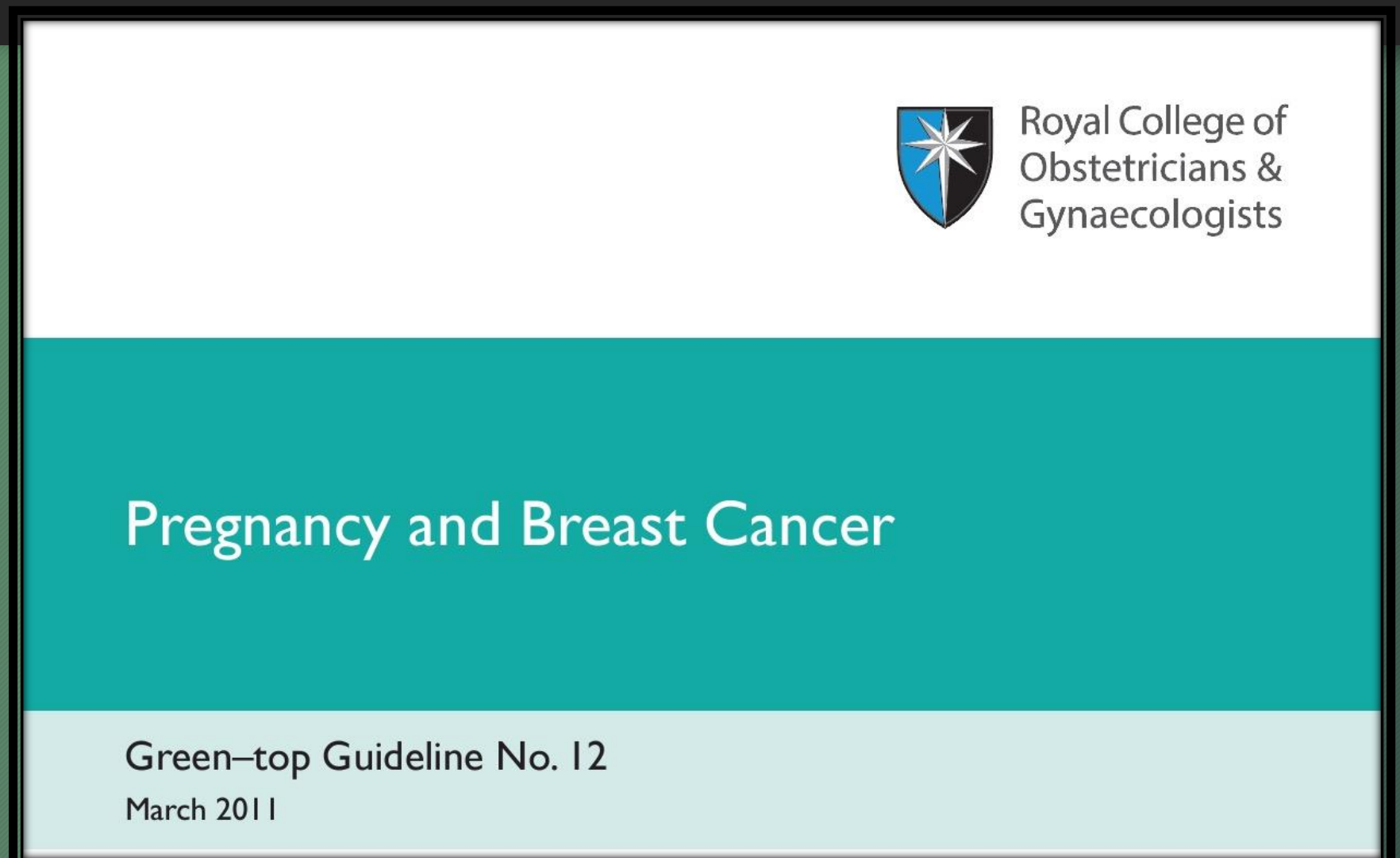
This is what you can expect an obstetrician to know from the confidential reports

- Investigate & treat in general as non-pregnant (manner, timescale & targets)
- BUT also proceed with appropriate caution eg lead screening and avoid specific known harms e.g. trastuzumab
- Vital to have an MDT especially in women with new & previous cancer & particularly across centres / hospitals
- Treating cancer does not usually require early delivery – unless there is a specific problem identified
- As the risk of recurrence in Ca Breast is highest in the 1st 2 years, recommend avoidance of pregnancy at this time

Especially in metastatic disease – send the placenta for histology



Dilemma: what to do?



There are gaps in the evidence base and advice is sometimes too vague and non-specific to help with individual patients – and practice has moved on?

Dilemma: ‘mother before baby’

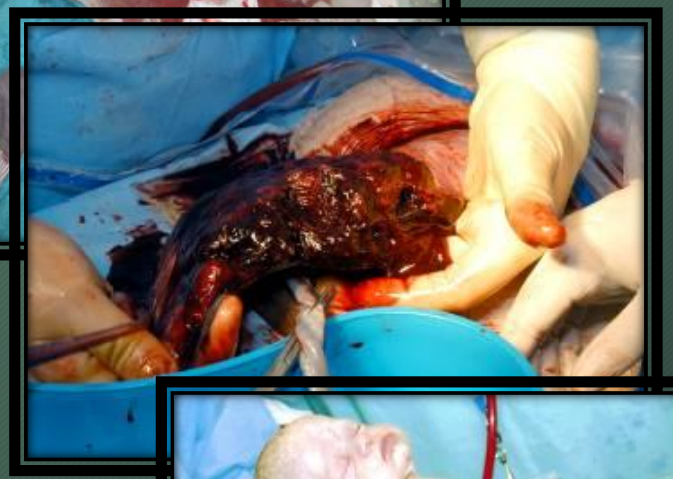
- Structured approach
- Call for help, ABC
- Resuscitation, primary survey
- Fetus
- Secondary survey, definitive care

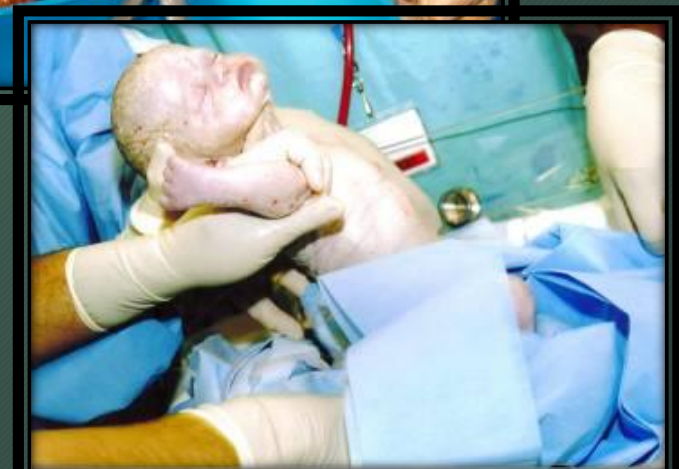
In an obstetric emergency, obstetricians are trained and used to a clear, sequential plan of assessment and action.

Dilemma: ‘mother before baby’

- Structured approach
- Call for help, ABC
- Resuscitation, primary survey
- Fetus
- Secondary survey, definitive care

Delivery may form part of the maternal resuscitation





Dilemma: pregnancy is inherently risky - maternal mortality rates

Obstet Gynecol. 2012 Feb;119(2 Pt 1):215-9. doi: 10.1097/AOG.0b013e31823fe923.

The comparative safety of legal induced abortion and childbirth in the United States.

Raymond EG[1], Grimes DA.

USA 1998-2005
Maternal mortality mothers of live neonates 8.8/100,000
Mortality rate for induced abortion 0.6/100,000

UK 2014
Maternal mortality similar
No deaths following abortion reported on form HSA4 in 2014

Abortion Statistics, England and Wales: 2014 DoH

One cannot manage pregnancy based purely on risk – pregnancy is about managing risk; this is what we do!

As an example, consider an adverse event that is increased both in pregnancy and in cancer: venous thromboembolism (VTE). Taking the OCC was 'safer' than not taking it and being pregnant. Risk is relative.

Dilemma: 'normal' pregnancy increases VTE risk

Background rate about 2/10,000 women/yr
Oral contraceptive 5-12/10,000 women/yr

RR pregnancy – 4-6 fold (more postpartum)

107/100,000 person years overall in pregnancy UK

BMI> 30 aOR 5.3; multiple pregnancy aOR 4.2;
caesarean section aOR 3.6

Faculty of Sexual & Reproductive Healthcare Statement; VTE & hormonal contraception, Nov 2014
Sultan AA *et al*. Br J Haematol 2012;156:366-73
RCOG GTG No 37a 2015

Dilemma: refusal of treatment

The process of consent in pregnancy may not be straightforward. Although we manage pregnancy with reference to potential risks and benefits of treating (or not treating) maternal or fetal conditions - the source of considerable litigation – a mother does not have to act on our advice or recommendation.

A competent pregnant woman has the right to refuse treatment even if that refusal may result in harm to her or her unborn child / Application of the Mental Health Act 1983

St George's Healthcare NHS Trust v S; R v Collins and others, ex parte S (1998) 3 All ER 673

The dilemma for a fetus

- The law does not identify the fetus as a person until birth
- But does recognise the fetus as unique and not part of the mother
- It is not possible to bring legal proceedings in the name of the fetus
- A fetus cannot be made a ward of court (but a newborn can)

See for example: Paton v BPAS Trustees (1979) QB 276

The dilemma for a fetus

THE FETUS IS NOT DIRECTLY PROTECTED BY THE EUROPEAN CONVENTION ON HUMAN RIGHTS

See for example: Vo. V. France (European Court of Human Rights) 2003

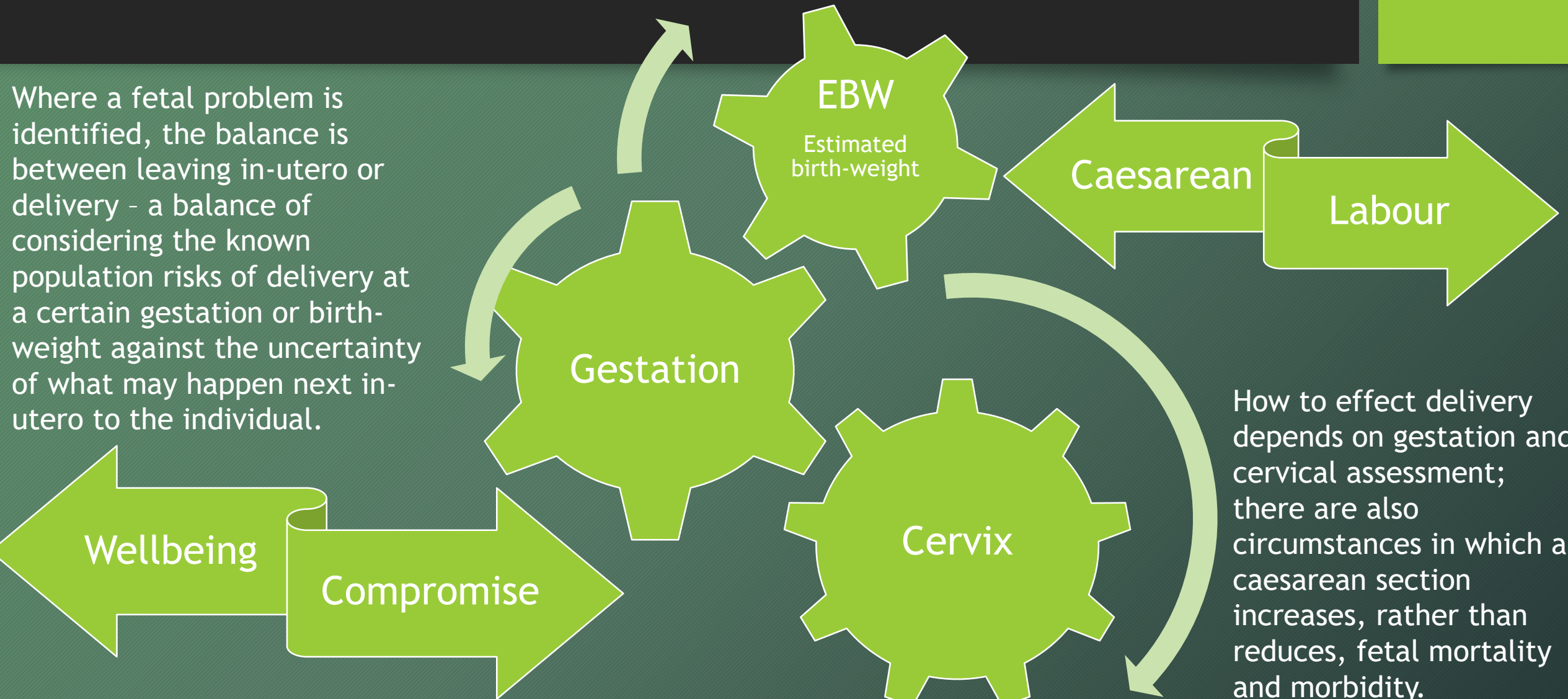
Fetal monitoring

- Growth
- Liquor
- Placental & fetal blood flows

A mother thinks constantly about her baby. Tests of fetal well-being in-utero are relatively limited - to assessment of fetal growth, doppler assessment of placental and fetal blood flows and indirect non-specific fetal kidney function / placental function (liquor volume). The acute condition is assessed by electronic fetal heart rate monitoring.

Dilemma: fetal concerns

Where a fetal problem is identified, the balance is between leaving in-utero or delivery – a balance of considering the known population risks of delivery at a certain gestation or birth-weight against the uncertainty of what may happen next in-utero to the individual.



How to effect delivery depends on gestation and cervical assessment; there are also circumstances in which a caesarean section increases, rather than reduces, fetal mortality and morbidity.

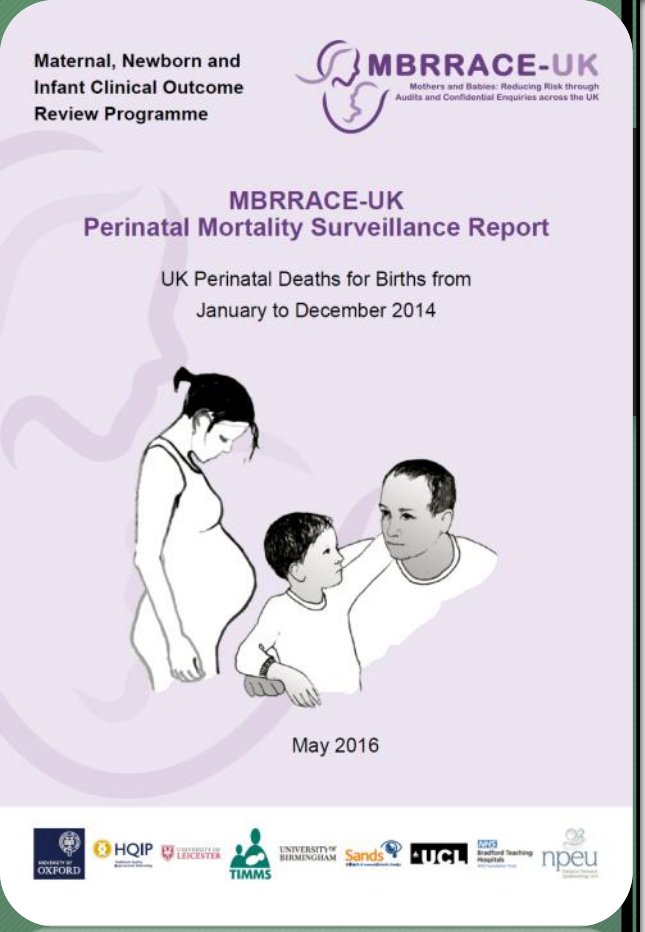


Table 4: Stillbirth, neonatal, and extended perinatal mortality rates (95% CIs) by gestational age at birth: United Kingdom and Crown Dependencies, for births in 2014

Rate per 1,000 births*	UK^	Gestational age at birth (weeks)				
		24+0-27+6	28+0-31+6	32+0-36+6	37+0-41+6	≥42+0
Stillbirths†	**4.12 (3.98 to 4.26)**	**(211.68 to 240.70)**	**(76.29 to 89.73)**	**(15.12 to 17.35)**	**(1.53 to 1.72)**	**(0.55 to 1.37)**
Antepartum†	*3.62 (3.48 to 3.75)*	*184.84 (171.37 to 198.30)*	*75.75 (69.30 to 82.19)*	*14.98 (13.91 to 16.06)*	*1.42 (1.33 to 1.51)*	*0.73 (0.37 to 1.09)*
Intrapartum†	*0.35 (0.31 to 0.39)*	*30.08 (24.15 to 36.00)*	*5.41 (3.62 to 7.20)*	*0.73 (0.49 to 0.97)*	*0.15 (0.12 to 0.18)*	*0.18 (0.00 to 0.36)*
Unknown timing†	*0.15 (0.13 to 0.18)*	*11.28 (7.61 to 14.94)*	*1.86 (0.81 to 2.90)*	*0.53 (0.32 to 0.73)*	*0.06 (0.05 to 0.08)*	*0.05 (0.00 to 0.14)*
Neonatal deaths‡	**1.76 (1.67 to 1.86)**	**155.47 (141.18 to 169.76)**	**30.68 (26.29 to 35.07)**	**6.28 (5.58 to 6.98)**	**0.70 (0.64 to 0.77)**	**0.46 (0.17 to 0.74)**
Early neonatal deaths‡	*1.23 (1.15 to 1.30)*	*106.88 (94.70 to 119.07)*	*22.76 (18.96 to 26.55)*	*4.63 (4.03 to 5.23)*	*0.46 (0.41 to 0.51)*	*0.41 (0.14 to 0.68)*
Late neonatal deaths‡	*0.54 (0.49 to 0.59)*	*48.58*	*7.92*	*1.65*	*0.24*	*0.05*
Perinatal deaths†	**5.34 (5.18 to 5.5)**	**308.90**	**103.88**	**20.80**	**2.09**	**1.37**
Extended perinatal deaths†	**5.88 (5.71 to 6.04)**	**346.49 (329.98 to 363.00)**	**111.15 (103.49 to 118.80)**	**22.42 (21.11 to 23.72)**	**2.33 (2.22 to 2.44)**	**1.42 (0.92 to 1.92)**

† per 1,000 total births

‡ per 1,000 live births

* excluding terminations of pregnancy, births <24+0 weeks gestational age and deaths with unknown gestation

^ including the Crown Dependencies

Data sources: MBRRACE-UK, NN4B, ONS, NRS, ISD, NIMATS, States of Guernsey, States of Jersey

There is a clear adverse relationship between prematurity and perinatal mortality, but what is a 'safe' gestation to undertake 'elective' (iatrogenic) delivery?

Welsh data

One must be careful in extrapolating data from all births when discussing fetal risks of mortality and morbidity for an individual. Looking at data from the All Wales Perinatal Survey, for example, the survival of a baby looks pretty good after 33 weeks, but this includes lots of babies born spontaneously, in whom the stress of labour helps mature the fetal lungs.

Table A6 Outcome by gestation in Wales: 2010 to 2014

Gestational Age	Registrable	Livebirths		Survivors up to one month after livebirth		Stillbirths (ind. terminations)	
	Total	Total	%	Total	%	Total	%
20	12	12	100.00	0	0.00	0	0.00
21	13	13	100.00	0	0.00	0	0.00
22	19	19	100.00	0	0.00	0	0.00
23	73	73	100.00	14	19.18	0	0.00
24	155	89	57.42	45	50.56	66	42.58
25	195	121	62.05	93	76.86	74	37.95
26	216	168	77.78	140	83.33	48	22.22
27	244	209	85.66	187	89.47	35	14.34
28	282	242	85.82	228	94.22	40	14.18
29	312	274	87.82	265	96.72	38	12.18
30	402	369	91.79	355	96.21	33	8.21
31	529	504	95.27	489	97.02	25	4.73
32	739	697	94.32	689	98.85	42	5.68
33	1,006	959	95.33	951	99.17	47	4.67
34	1,640	1,602	97.68	1,588	99.13	38	2.32
35	2,395	2,340	97.70	2,325	99.36	55	2.30
36	4,644	4,601	99.07	4,585	99.65	43	0.93
37	9,939	9,889	99.50	9,871	99.82	50	0.50
>37	151,440	151,199	99.84	151,089	99.93	241	0.16
Unknown	1,150	1,147	99.74	1,143	99.65	3	0.26
Total (incl. Unknown)	175,405	174,527	99.50	174,057	99.73	878	0.50

Source: NCCHD & AWPS/MBRRACE-UK

For outcome by gestation in the total number of stillbirths includes late termination

Dilemmas – caesarean section not always safest & lung maturity depends on labour

What constitutes 'term' from a lung maturity view point depends on the mode of delivery – first shown by John Morrison at Cambridge. Up until this point we knew that steroids reduce respiratory distress syndrome, but the apparent loss of effect after 34 weeks was because vaginal births skewed the outcomes. Looking at RDS in elective caesarean births showed a different story.....

Surfactant production from 28 weeks

Antenatal steroids reduce perinatal mortality & RDS

Effect falls after 34 weeks (still present)

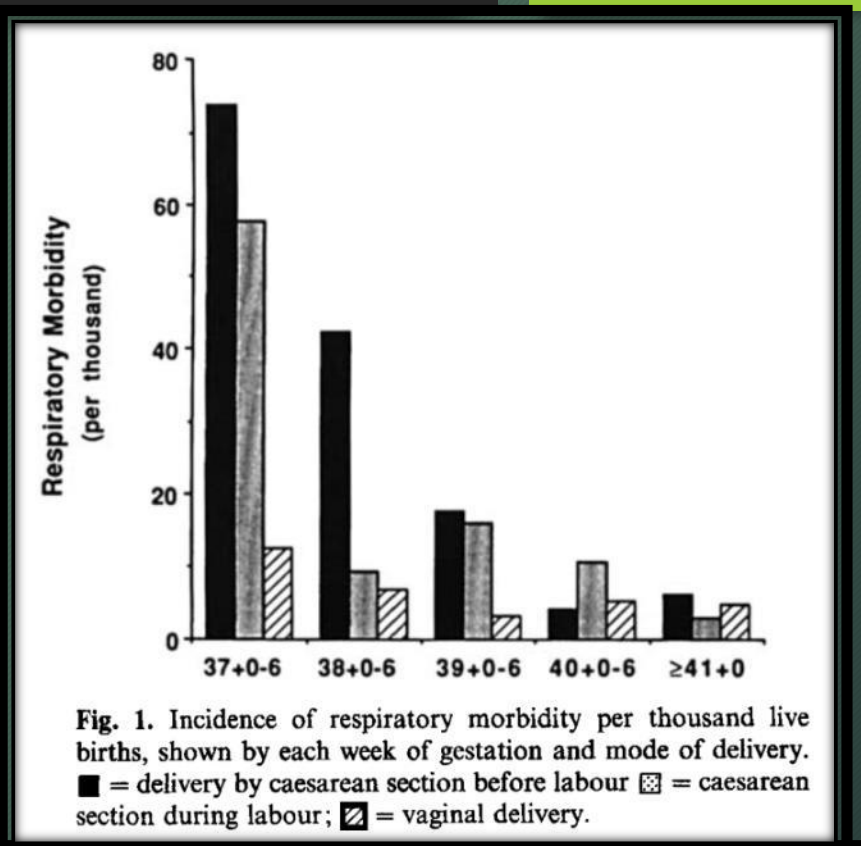


Fig. 1. Incidence of respiratory morbidity per thousand live births, shown by each week of gestation and mode of delivery. ■ = delivery by caesarean section before labour ▩ = caesarean section during labour; ▨ = vaginal delivery.

Morrison JJ, Rennie JM, Milton PJ BJOG 1995;102 (2): 101-6
Stutchfield P, Whitaker R, Russell I BMJ 2005; 331:662

Dilemmas – caesarean section not always safest & lung maturity depends on labour

The default position for elective c/section is therefore to aim for delivery at 39 completed weeks if possible to minimise fetal morbidity and mortality. An RCT run from Glan Clwyd Hospital in north Wales, showed that antenatal steroids halved the rate of RDS for elective c/section performed under 39 weeks, but did not eliminate the risk.

Stress (labour) increases surfactant

Increased RDS by elective caesarean section vs vaginal delivery at 'term'

Effect disappears at 39 weeks & steroids half the risk

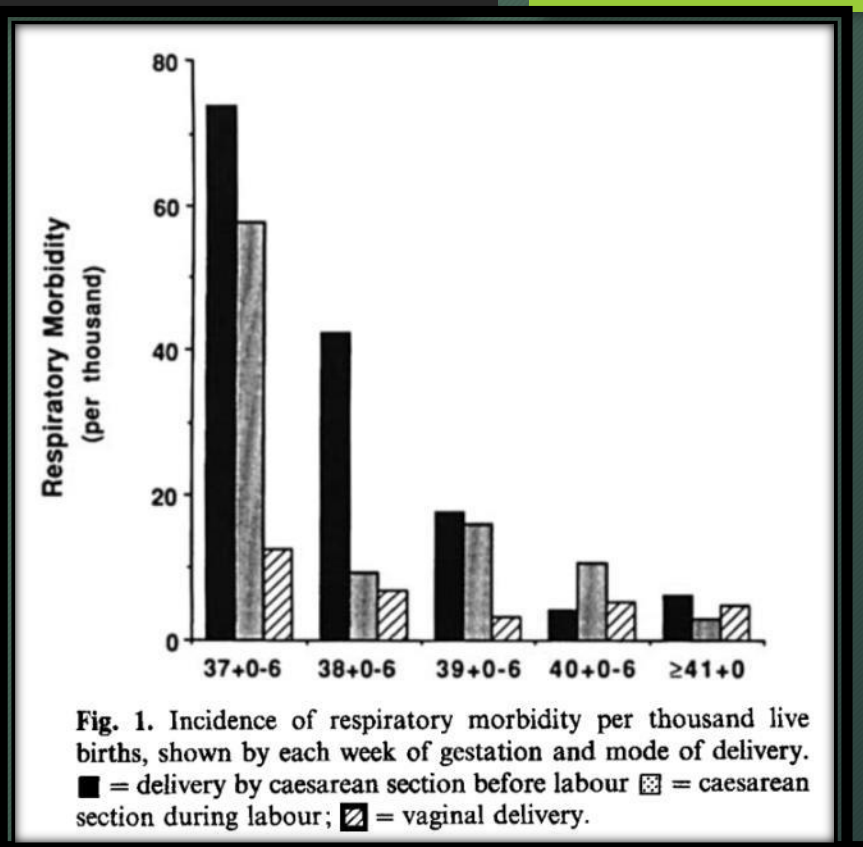


Fig. 1. Incidence of respiratory morbidity per thousand live births, shown by each week of gestation and mode of delivery. ■ = delivery by caesarean section before labour ▨ = caesarean section during labour; ▨ = vaginal delivery.

Morrison JJ, Rennie JM, Milton PJ BJOG 1995;102 (2): 101-6
Stutchfield P, Whitaker R, Russell I BMJ 2005; 331:662

Consent – where are we in obstetrics?

This makes describing risk in consent for delivery more difficult. Furthermore, we can no longer take consent based just on what other doctors think is right, but we must discuss all risks that a woman may find important, both as an individual and in general.

Used not to be judged negligent if the information given to a patient about a treatment or procedure was that of a responsible body of medical opinion, provided the standard was considered reasonable by a Court.

Montgomery: risk of shoulder dystocia in pregnancy for a baby diagnosed as being big was not explained clearly – doctor knew serious but rare and did not discuss in terms of offering alternative (c/section) to avoid. The baby had a shoulder dystocia with physical injury as a consequence.

Bolam v Friern Hospital Management Committee [1957] 1 WLR 582
Montgomery v Lanarkshire Health Board [2015] UKSC 11
Consent: patients and doctors making decisions together, GMC, 2008 paragraphs 28-36

After the Montgomery ruling...

Need to discuss when “a reasonable person in the patient’s position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it.“

- Emphasis switched to patient expectations

Doctors should focus their discussions on the patient’s individual situation and risk to them and are required to tell patients if an investigation or treatment might result in a serious adverse outcome, even if the likelihood is very rare

- An assessment of the individual

Montgomery v Lanarkshire Health Board [2015] UKSC 11

Not always easy in obstetrics –'normality' & capacity

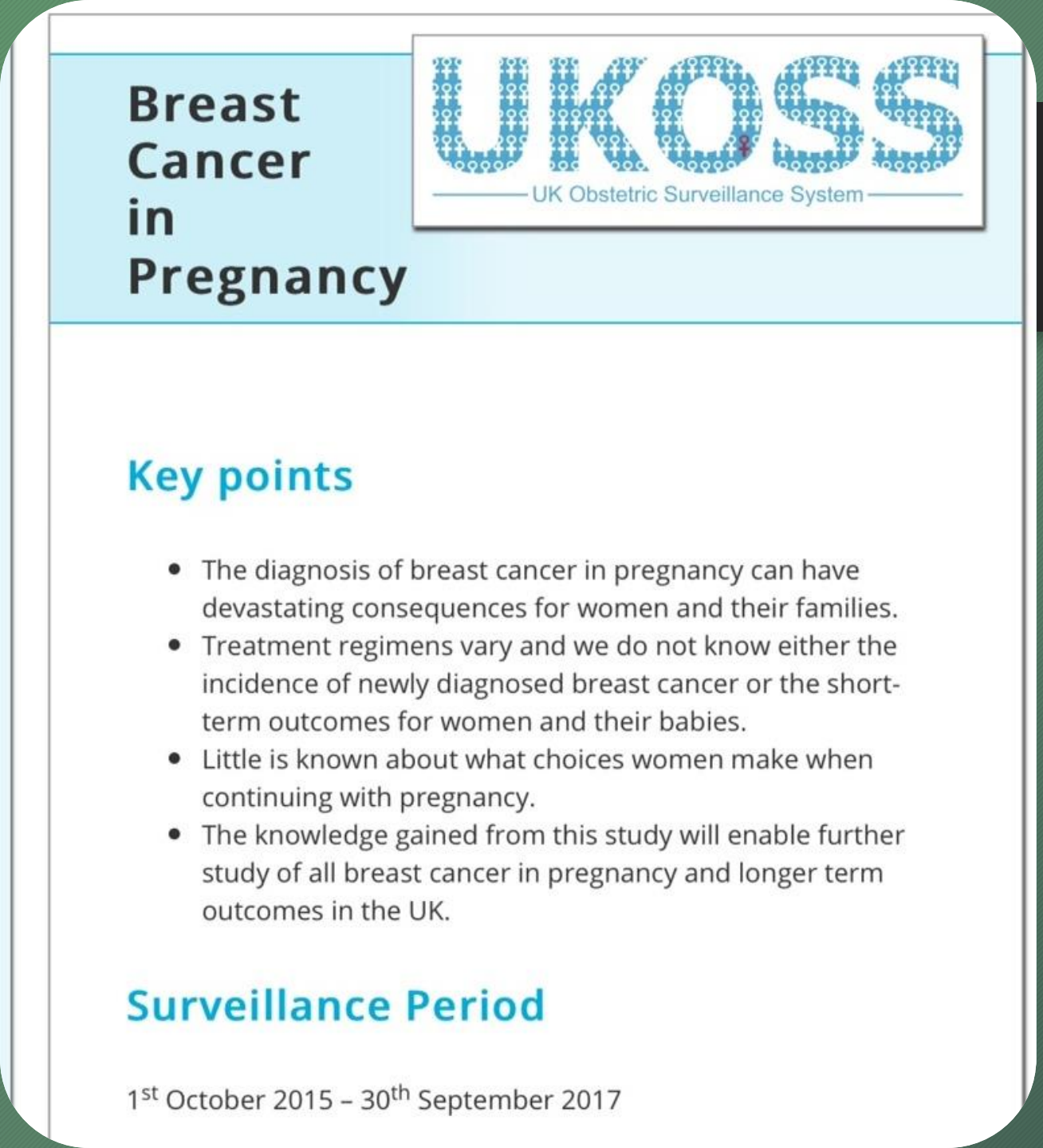
We may not really know the 'right' way to consent women with cancer in pregnancy or when the 'right' time to deliver an individual may be? In pregnancy, as most women are normal, we are wary of talking too bluntly about what can go wrong. Furthermore, when an emergency arises, pain and opiates affect capacity to consent and sometimes our decisions in obstetrics have to be immediate. (So it can be a bit of a minefield - we are actively studying capacity in obstetric emergencies currently).

Most women are normal

Assessing capacity formally takes about 2 hours

Many women in labour are unable to recall any risks of complications – pain / opiates / altered mental state

Mental Capacity Act 2005, Section1, an adult is unable to make a decision if he or she does not have the capacity to consent and one part of capacity is that the person should be able to **retain** the information provided



So we have seen that although there may be rough guidance on the management of women with breast cancer in pregnancy – investigate and treat as if non-pregnant - we do in practice vary what we do to account for (and try to avoid) things we believe to be harmful to the fetus, with variation therefore in diagnosis and treatment as a consequence. We have also seen that the recommendation not to deliver the baby early can be open to variation in interpretation and application, with potential adverse consequences to the newborn.

In order to find out more about practice in the UK, we are in the middle of the UK Breast Cancer in Pregnancy Study.

Breast Cancer in Pregnancy

UKOSS
UK Obstetric Surveillance System

Case definition

Any woman meeting one of the following criteria:

- Newly diagnosed case of breast cancer during pregnancy.
- First pathological diagnosis of breast cancer during pregnancy.
- A new confirmed diagnosis of breast cancer during pregnancy determined from the medical records.

Excluded:

- Breast cancer diagnosed before pregnancy.
- Recurrence of breast cancer in current pregnancy.

All maternity units in the UK complete and return a notification card of current UKOSS studies EVERY MONTH – even if there are no cases to report. The data collection forms are then sent by UKOSS to the local unit's named reporter. No patient identifiable data are submitted.

Funding

This study is being funded by the Betsi Cadwaladr University Health Board (BCUHB).

Ethics committee approval

This study has been approved by the North London REC1 (REC Ref. Number: 10/H0717/20).

Lead Investigator

Philip Banfield, Claudia Hardy, BCUHB North Wales; Julie Jones, North Wales Cancer Centre; Sarah Davies, Lynda Sackett, BCU Health Board North Wales; Marian Knight, NPEU

Research questions

- What is the current incidence of primary breast cancer in pregnancy in the UK?
- How does breast cancer present and at what gestation?
- How is breast cancer managed in pregnancy in the UK?
- Is there variation in the timing of surgical intervention?
- What are the short-term outcomes for mother and infant?

51 cases reported (5 in error)

21 data collection forms - well-completed

In the first 13 months, we are probably a few cases under-reported. The notification comes first, but the completed form follows only after delivery.

The individual UKOSS reporters are returning the forms with a high degree of completion. There is a section on the oncology aspects of each case, which breast cancer teams have been helping with – thank you.

Section 6: Outcomes
Section 6a: Woman

6a.1 **Was the woman admitted to ITU or level 3 care?** Yes ☐ No ☐

If Yes, please specify duration of stay: ☐☐ *days*

OR Tick if woman is still in ITU or level 3 care: ☐

OR Tick if woman was transferred to another hospital: ☐

6a.2 **Did any other major maternal morbidity occur?**[5*] Yes ☐ No ☐

If Yes, please specify: _____

6a.3 **Did the woman die?** Yes ☐ No ☐

If Yes, please specify date and time of death D D / M M / Y Y h h : m m

What was the primary cause of death as stated on the death certificate?
(Please state if not known.) _____

Section 6b: Infant 1

NB: If more than one infant, for each additional infant, please photocopy the infant section of the form **(before filling it in)** and attach extra sheet(s)

6b.1 **Date and time of delivery:** D D / M M / Y Y h h : m m

6b.2 **Mode of delivery:**

Spontaneous vaginal ☐ Ventouse ☐ Lift-out forceps ☐ Rotational forceps ☐

Breech ☐ Pre-labour caesarean section ☐ Caesarean section after onset of labour ☐

6b.3 **Birthweight:** ☐☐☐☐ *g*

6b.4 **Sex of infant:** Male ☐ Female ☐ Indeterminate ☐

6b.5 **Did the infant have any congenital anomalies?** Yes ☐ No ☐

If Yes, please specify: _____

6b.6 **Was the infant stillborn?** Yes ☐ No ☐

If Yes, *please go to section 7.*

6b.7 **5 min Apgar** ☐☐

6b.8 **Was the infant admitted to the neonatal unit?** Yes ☐ No ☐

If Yes, what was the reason for admission?

Neutropaenia ☐ IUGR ☐ Congenital malformation ☐

Other *(please specify)* _____ ☐

6b.9 **Did any other major infant complications occur?**[6*] Yes ☐ No ☐

If Yes, please specify: _____

6b.10 **Was breastfeeding initiated?** Yes ☐ No ☐ Not known ☐ Not applicable ☐

6b.11 **Was lactation suppression used?** Yes ☐ No ☐

6b.12 **Did this infant die?** Yes ☐ No ☐

If Yes, please specify date and time of death D D / M M / Y Y h h : m m

What was the primary cause of death as stated on the death certificate?
(Please state if not known) _____

Section 10: Therapy

10.1 **Did the patient undergo surgery for breast cancer during pregnancy?** Yes ☐

No, surgery not recommended ☐

No, surgery delayed until the end of pregnancy ☐

If Yes, please select surgery type and date of surgery

Breast conservation ☐ D D M M Y Y

Mastectomy ☐ D D M M Y Y

Other, please specify _____ ☐ D D M M Y Y

10.2 **Did this patient undergo radiotherapy during pregnancy?** Yes ☐

No, radiotherapy not recommended ☐

No, radiotherapy delayed until end of pregnancy ☐

If Yes, please state start date and end date of radiation therapy

Start D D / M M / Y Y End D D / M M / Y Y

10.3 **Did this patient have systemic (chemo-) therapy during pregnancy?** Yes ☐

No, systemic (chemo-) therapy not recommended ☐

No, systemic (chemo-) therapy delayed until end of pregnancy ☐

If Yes, please state type of treatment

Primary (neo-adjuvant) ☐

Adjuvant ☐

Metastatic ☐

Not known ☐

Please give dates:

Start of systemic (chemo-) therapy D D M M Y Y

End of systemic (chemo-) therapy D D M M Y Y

Please detail drug(s) used during pregnancy *(please tick all that apply)*.

Doxorubicin (Adramycin)	☐	Trastuzumab (Herceptin)	☐
Cyclophosphamide	☐	D	
Paclitaxel	☐	I	
Epirubicin	☐	2	
Methotrexate	☐	-	
Other – please specify			

10.4 **Was the woman hospitalised due to complicatio**

Yes, other *(plea*

10.5 **Was systemic (chemo-) therapy given postpartu**

Section 11: Complications during pregnancy related to breast cancer or therapy for breast cancer

11.1 **Were there any complications during pregnancy related to breast cancer or therapy for breast cancer?** Yes ☐ No ☐

If Yes, please tick any of the following that apply:

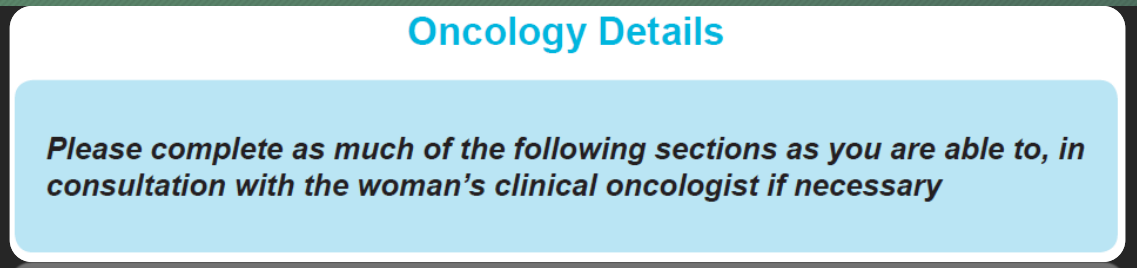
Neutropenic sepsis	☐	Heart failure	☐
Pancytopenia	☐	Cardiac arrest	☐
Cardiomyopathy	☐	Uncontrolled emesis	☐
Polyhydramnios	☐	Thromboembolism	☐
Oligohydramnios	☐	Other – please specify	☐

11.2 Did the woman have metastatic disease later in pregnancy? Yes ☐ No ☐

If Yes, where: _____

The UKOSS methodology is well established amongst obstetricians, midwives and obstetric anaesthetists and physicians, collecting anonymised data.

Picking up all cases



It is hugely important to capture all cases during the study period (1/10/15 – 30/9/17). We need assistance to pick up cases that have ended in miscarriage or termination if possible, too, so need help from the breast cancer community, please. Letting us know there is a case and where the maternity unit is helps UKOSS to get the form to the right place while maintaining anonymity from the study team.

All cancer centres in the UK – normal UKOSS reporting.

Clinicians with a case can contact:
Claudia.hardy@wales.nhs.uk;
Philip.banfield@wales.nhs.uk

Or ukoss@npeu.ox.ac.uk (cc'd to us, please)

NPEU will put in touch with local UKOSS reporter - this approach works