Joint Committee on the Eighth Amendment of the Constitution

Termination of Pregnancy a Fetal Medicine Perspective

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Background

I am a consultant in Maternal and Fetal medicine at Birmingham Women's and Children's Hospital. I qualified as a doctor and trained as an Obstetrician and Gynaecologist in London, working with Professors Greenough and Nicholaides, with whom I performed research on antenatal lung development. Subsequently I worked as a Lecturer at The Royal Free Hospital.

In 1999 I moved to Birmingham as a Consultant in Maternal and Fetal Medicine. I am an active clinician and perform two fetal medicine lists per week as well as being the lead clinician for women with cardiac disease in pregnancy, women with a multiple pregnancy and the Day Assessment Unit.

Birmingham Women's and Children's Hospital is the regional centre for the West Midlands for Fetal Medicine. We deliver over 8000 babies each year and last year in the fetal medicine unit we performed over 7000 ultrasound scans, 410 invasive procedures for checking fetal chromosomes, 48 intrauterine blood transfusions, 39 fetoscopic laser ablations, a number of other invasive procedures and selective reductions. The unit is a supraregional referral centre for the management of Fetal Fetal Transfusion Syndrome and its management by fetoscopic laser ablation. More details of our workload can be found at http://www.bwnft.nhs.uk/wp-content/uploads/2015/05/The-Fetal-Medicine-Centre-Annual-Report-16-17.pdf

Forty years ago the Westminster Parliament passed a private members bill ensuring that doctors who performed abortions under certain circumstances, would not be performing an unlawful act. This law was brought into use in England, Wales and Scotland, but has never been adopted in Northern Ireland. It was subsequently amended by the Human Fertilisation and Embryology Act 1990, however despite subsequent attempts no further amendments have been passed. Therefore it is still an offence to procure an abortion unless two independent medical practitioners are of the opinion, formed in good faith, that the case

meets at least one of the criteria below. There is however one exception to this, when an emergency termination of pregnancy is required in order to immediately save the woman's life, or to prevent grave permanent injury to the physical or mental health of the pregnant woman. In these rare scenarios, only 11 cases in England and Wales in the last 10 years, a single medical practitioner's signature is required. More than one of these criteria can be met in any individual case.

Clauses for Termination of Pregnancy as amended by the 1990 HFEA Act

A. The continuance of the pregnancy would involve risk to the life of the pregnant woman greater than if the pregnancy were terminated
B. The termination is necessary to prevent grave permanent injury to the physical or mental wellbeing of the woman
C. The pregnancy has NOT exceeded its 24th week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman
D. the pregnancy has NOT exceeded its 24th week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of any existing child(ren) of the family of the pregnant woman
E. There is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped.

It is important to note that only clauses C and D are gestation dependant. All figures quoted are from the Office of National Statistics or the Central Statistics Office of the Republic of Ireland. In 2014 there were approximately 871,000 conceptions in England and Wales, with 697,000 births. In comparison the number of births in Ireland was 67,000 for the same time period, that is approximately 10% of that of England and Wales. There were 190,406 abortions performed in England and Wales in 2016[1] the most recent data available.

Legal Abortions England and Wales 2016 by Clause

England and Wales, residents					numbers
	Gestation weeks				
Grounds	Total	3 - 9	10 - 12	13 - 19	20 and over
Total abortions	**185,596**	**149,825**	**20,000**	**12,738**	**3,033**
A (alone, or with B, C, D) or F or G	**105**	23	9	46	27
B (alone, or with C or D)	**147**	94	27	20	6
C (alone)	**180,794**	148,738	19,347	10,785	1,924
D (alone, or with C)	**1,342**	947	270	118	7
E (alone, or with A, B, C or D)	**3,208**	23	347	1,769	1,069

Abortion for Fetal Abnormality

Of all these abortions however, only 3208 were performed under clause E, ie where there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped. There is a slight issue with some of these figures however as it has been reported that larger numbers of fetal anomalies that undergo abortion have been reported to the congenital abnormalities register, with a three year audit suggesting that only 54% of such cases were reported to the Department of Health. Therefore this figure may be higher.

Although, as in the Republic of Ireland the main fetal anomaly ultrasound is performed at approximately 20 weeks gestation, it can be seen from the table below that only 507 of these abortions were performed after 22 weeks gestation. In 2016, 141 terminations were selective terminations of pregnancy, involving multiple pregnancies and over three quarters of these were under clause E. As can be seen from one of the case studies attached these procedures can have significant benefit for the co-twin.

Gestational age at time of termination of pregnancy England and Wales 2016 Clause E

England and Wales, residents — percentages

Procedure	Total	Gestation weeks for abortions performed under ground E: under 13	13 & 14	15 & 16	17 to 19	20 & 21	22 and ove
Total abortions	**3,208**	**370**	**798**	**523**	**448**	**562**	**507**
Surgical	***29***	***58***	***44***	***34***	***19***	***7***	***10***
Vacuum Aspiration	***12***	*43*	*28*	*0*	*0*	*0*	*0*
Dilatation and Evacuation	***13***	*8*	*13*	*31*	*16*	*6*	*3*
Feticide with a surgical evacuation [1]	***4***	*7*	*3*	*3*	*2*	*2*	*8*
Medical	***71***	***42***	***56***	***66***	***81***	***93***	***90***
Antiprogesterone with or without prostaglandin	***54***	*42*	*56*	*65*	*76*	*75*	*7*
Other medical agent	***1***	*0*	*0*	*1*	*4*	*2*	*1*
Feticide with a medical evacuation [2]	***16***	*0*	*0*	*0*	*1*	*16*	*81*

[1] includes feticide with no method of evacuation and surgical 'other'.
[2] includes 89 cases where use of feticide was not confirmed at time of publication.

The indications for Abortion under clause E are predominantly for a chromosomal or central nervous system difference, with these two factors accounting for 57% of all cases. The commonest chromosomal difference identified as a reason for abortion was Trisomy 21, which is not surprising given the prevalence of this condition and the established antenatal screening programme in England. The clinical indications for these terminations of pregnancy can be seen below.

Clinical Indications For Termination of Pregnancy under Clause E

England and Wales, residents — numbers and percentages

ICD-10 code	Condition	Number of abortions by principal medical condition		Number of mentions by principal medical condition		24 weeks gestation and over	
		number	%	number	%	number	%
Total ground E alone or with any other [1]		**3,208**	**100**	**3,873**	.	**225**	**100**
Q00-Q99	**Congenital malformations total**	**1,471**	**46**	**1,926**	**50**	**154**	**68**
Q00-Q07	**the nervous system total**	**680**	**21**	**844**	**26**	**83**	**37**
Q00	anencephaly	219	7	228	7	4	2
Q01	encephalocele	31	1	41	1	1	0
Q02	microcephaly	6	0	10	0	3	1
Q03	hydrocephalus	20	1	33	1	3	1
Q04	other malformations of the brain	118	4	176	5	22	10
Q05	spina bifida	177	6	199	6	9	4
Q06-Q07	other	109	3	157	5	41	18
	Other congenital malformations	**791**	**25**	**1082**	**34**	**71**	**32**
Q10-Q18	the eye, ear, face and neck	5	0	6	0	0	0
Q20-Q28	the cardiovascular system	288	9	395	12	27	12
Q30-Q34	the respiratory system	21	1	32	1	1	0
Q35-Q37	cleft lip and cleft palate	9	0	22	1	0	0
Q38-Q45	other malformations of the digestive system	6	0	10	0	0	0
Q60-Q64	the urinary system	102	3	148	5	9	4
Q65-Q79	the musculoskeletal system	246	8	333	10	24	11
Q80-Q85	the skin, breast integument phakomatoses	14	0	17	1	1	0
Q86-Q89	other	100	3	119	4	9	4
Q90-Q99	**Chromosomal abnormalities total**	**1,187**	**37**	**1,244**	**39**	**46**	**20**
Q90	Down's syndrome	706	22	730	23	21	9
Q910-Q913	Edwards' syndrome	220	7	231	7	6	3
Q914-Q917	Patau's syndrome	84	3	86	3	5	2
Q92-Q99	other	177	6	197	6	14	6
	Other conditions total	**550**	**17**	**703**	**22**	**25**	**11**
P00-P04	fetus affected by maternal factors	197	6	259	8	3	1
P05-P08	fetal disorders related to gestation and growth	30	1	41	1	10	4
P35-P39	fetus affected by congenital infectious disease	0	0	0	0	0	0
P529	intracranial nontraumatic haemorrhage of fetus	2	0	3	0	1	0
P832-P833	hydrop fetalis not due to haemolytic disease	77	2	113	4	5	2
O30	multiple gestation	48	1	52	2	0	0
O41	disorder of the amniotic fluid	10	0	14	0	0	0
Z20-Z22	exposure to communicable disease	5	0	5	0	3	1
Z80-Z84	family history of heritable disorder	26	1	30	1	1	0
D181	Cystic Hygroma (Lymphangioma)	94	3	124	4	1	0
E84	cystic fibrosis	9	0	9	0	1	0
G71	disorder of the muscles	13	0	13	0	0	0
	other [3]	18	1	19	1	0	0
	not known *	21	1	21	1	0	0

[1] ICD-10 codes are taken from the International Statistical Classification of Diseases and Related Health problems (Tenth Revision) published by the World Health Organisation (WHO)

[2] the all mentions totals show abortions where more than one medical condition is reported. Totals therefore do not equal the number of abortions performed under Ground E
additional breakdown may be available by ICD-10 code on request.

[3] There was an additional 1 case not performed under Ground E at 24 weeks and over gestation making the total 226, see table 5

* Cases where diagnosis is' not known' are being followed up

Note: percentages are rounded and may not add up to 100

I note with interest that in previous discussions there has been debate with regard to the percentage of women who request a termination of pregnancy when their fetus has Trisomy 21. This is a complex scenario as I would expect that this number would be high. The reason for this is that women who undergo screening for trisomy 21 are a subset of the population at large, a self-selected group not representative of the population. Indeed our laboratories, which are one of the largest screening laboratories in the UK note that the acceptance of screening is approximately 60-70%. The women who are screen positive are then offered an invasive test, with a 1% risk of miscarriage. There are only three reasons to perform invasive testing in this context;

1. Women who are considering termination of pregnancy if the result shows that the fetus does have trisomy 21
2. Fetuses with other differences whose management following birth will change depending on the karyotype
3. Women who want this for information only

Therefore women who accept an invasive test are a further subset of the general population, who not surprisingly have a high rate of choosing option 1. Indeed if counselling prior to performing the initial screening test is good almost 100% of women who are screen positive should be expected to have an invasive test such as amniocentesis. These women will then make a decision re continuation of their pregnancy. The audit data from our laboratory screening 68875 pregnancies suggests that 66% of women who have prenatal diagnosis of a fetus with trisomy 21 opt for termination of pregnancy and around 9% have spontaneous miscarriages. Of note is the fact that the follow up data is not complete.

COMBINED	Affected pregnancies	Detected by screening	Medical terminations	Spontaneous termination	Confirmed live birth
T21	76	67	44	6	13
T18	30	28 (2 FN were increased risk for T21)	19	3	2
T13	13	11	5	6	0

The Irish Experience

Of the 4810 women who underwent termination of pregnancy in England and Wales whose post code was outside those two countries, 68% were from Ireland and a further 15% from Northern Ireland. Of the 3265 citizens of Ireland 141 women travelled to England or Wales, most commonly Liverpool, London or Birmingham in order to have an abortion under clause E of the Act. The fetal indications for these abortions are shown below.

Again, as with all cases aborted under clause E, there is preponderance for chromosomal differences and differences of the nervous system.

Indications for termination of pregnancy under clause E 2016 Irish residents

Irish Republic residents

		principal mentions	number of mentions
Total ground E alone or with any other [1]		**135**	
Q00-Q07	**the nervous system total**	**57**	**87**
Q00	anencephaly	7	8
Q01	encephalocele	2	2
Q02	Microcephaly	1	1
Q03	hydrocephalus	3	3
Q04	other malformations of the brain	1	2
Q05	spina bifida	9	10
Q06-Q07	other	0	4
Q20-Q28	the cardiovascular system	10	19
Q35-Q37	cleft lip and cleft palate	0	1
Q38	Congenital malformations of digestive system	0	1
Q60-Q64	the urinary system	4	8
Q65-Q79	the musculoskeletal system	13	19
Q86-Q89	other	7	9
Q90-Q99	**Chromosomal abnormalities total**	**69**	**72**
Q90	Down's syndrome	40	42
Q910-Q913	Edwards' syndrome	13	13
Q914-Q917	Patau's syndrome	7	7
Q92-Q99	other	9	10
	other conditions total	**9**	**10**
P00-P04	fetus affected by maternal factors	1	1
P05-P08	fetal disorders related to gestation and growth	0	0
P83.2-P833	hydrop fetalis not due to haemolytic disease	1	1
O30	multiple gestation	2	2
E849	Cystic fibrosis	1	1
G71.0	disorder of the muscles	1	1
D18.1	Cystic Hygroma (Lymphangioma)	3	4

ICD-10 codes are taken from the International Statistical Classification of Diseases and Related Health problems (Tenth Revision) published by the World Health Organisation (WHO)

Care Pathway for women with a diagnosed Fetal Abnormality

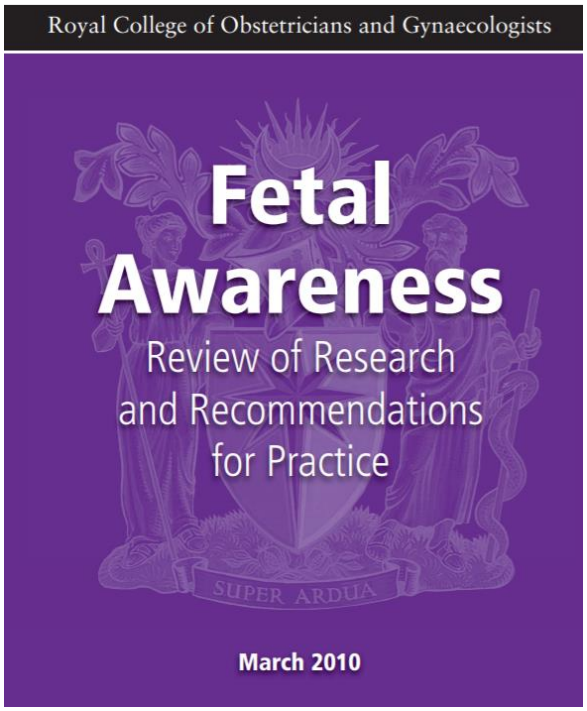
As explained in previous sessions detailed anomaly scans of fetuses are performed at approximately 20 weeks gestation, though the availability of this is limited in Ireland. In England and Wales if a difference is found in a fetus, a pathway is followed that may include a second local scan to confirm the diagnosis by an Obstetrician with a special interest in fetal medicine. This second scan should be performed within 5 working days. In some cases these local Obstetricians will be able to fully counsel women regarding the outlook for her baby, and in others, referral to a recognised fetal medicine unit will take place. We attempt to see women within three working days of referral and patients are scanned by a specialist in fetal

medicine and then sat in a more homely room and counselled in the presence of a midwife. All options are discussed with the women including, where appropriate, intrauterine fetal therapy and termination of pregnancy. On leaving the woman is given a detailed report which is read through with her prior to her leaving and contact numbers for the fetal medicine centre are given. A subgroup of women may need additional investigations, both invasive and non-invasive and some will require counselling by a specialist in another field. It is important to acknowledge that women will need differing amounts of time to come to terms with this information and make their decisions.

If the woman opts for termination of pregnancy this will be arranged at her local unit and depending on the gestational age both surgical and medical termination techniques are discussed with these women. As there is an increasing chance of fetuses being born alive after 22 weeks gestation the Royal College of Obstetricians and Gynaecologists recommends that the fetal heart is stopped by performing feticide prior to the termination for cases after 22 weeks gestation unless the fetal abnormality is not compatible with life[2].

Feticide is achieved by placing a needle, under ultrasound control through the maternal abdomen and uterus and into the blood vessels of the baby. The baby is then administered a neuromuscular blocker, to prevent it moving off the needle, in the same fashion as is administered to adults undergoing surgery, and the fetus is then injected with either potassium chloride or lidocaine, both of which stop the heart beating. Confirmation that the fetal heart has stopped is performed at 5 and 45 minutes. If the woman has opted for a medical termination of pregnancy a tablet, an anti-progestagen, is administered and admission arranged for induction of labour with prostaglandin, approximately 36 hours later. Around 95% of women will deliver on the day they receive their prostaglandins. A small proportion will require a second course and infection, haemorrhage and retained placental tissue are the main short term complications of the procedure. In our unit we complete the termination process in Birmingham, but once discharged the women return to Ireland. Whilst in Birmingham, they often express the difficulties that they have with regard to the limited number of people that they can discuss this scenario with.

Fetal awareness is a consideration at this time and something that both parents and professionals consider carefully. At what gestation fetuses will feel pain is debatable, however the Royal College of Obstetricians and Gynaecologists have produced a document summarising the best evidence as to when this is present. Their conclusion was that "*the evidence that the fetus can and does experience pain is less compelling and accordingly the benefit of administering analgesia is less evident, while the risks and practicalities of so doing remain. So on the basis of 'first do no harm', prior to the procedures described in this report, analgesia is no longer considered necessary, from the perspective of fetal pain or awareness.*"[3]



In our unit when women who are beyond 24 weeks gestation request termination of pregnancy we have a multidisciplinary meeting to gain a consensus as to whether we believe that "*there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped*". These meetings as a minimum require a hospital manager, 2 clinicians capable of performing the procedure, at least one neonatologist and at least one fetal medicine midwife.

If termination is to be performed surgically this requires a clinician with a certain skill set and appropriate referral to these clinicians is made. Often after surgical termination post-mortem results are not available. We generally recommend that post mortems are performed on fetuses that are terminated because of a structural difference as in up to 70% of cases a perinatal pathologist will detect additional information which often leads to a change in counselling.

Regardless of the mode of termination of pregnancy it is considered good practice to offer women follow up appointments to discuss events, answer any questions and explain the risk to future pregnancies. This is a service that Irish women tend not to receive from our unit.

Fatal Abnormalities

One of the issues that you face is the decision regarding which, if any, fetal abnormalities will be compliant with the new legislation for termination of pregnancy. With regard to this I would urge you not to make a list, as with the ever changing progress in medicine, conditions would need to be added and removed from the list on a regular basis. I would also strongly advise against being prescriptive and using the term lethal abnormality. The problem is there is no agreed definition as to what lethal actually means, is it that all fetuses with that condition die before birth, that they die either before birth or in the neonatal period despite supportive therapy, a baby that usually dies in one of these two periods of time or is it that it has been noted that there is an association between the condition and death. I have taken two tables from a paper by Wilkinson et al[4] for your information. The first of these, to the left, lists the commonest conditions named in the medical literature which have been said to be lethal fetal malformations. The same

Table 1. Malformations cited in lists of LM (arranged in descending order of frequency of citation)[7,16,18,23–25,38,56–58]

Lethal malformations
Potter's syndrome/renal agenesis
Anencephaly/acrania
Thanatophoric dwarfism
Trisomy 13 or 18
Holoprosencephaly
Triploidy
Hydranencephaly
Some cases of hypoplastic left heart syndrome and pentalogy of Cantrell
Severe osteogenesis imperfecta
Multicystic/dysplastic kidneys
Polycystic kidney disease
Congenital severe hydrocephalus with absent or minimal brain growth
Severe congenital diaphragmatic hernia with hypoplastic lungs
Sirenomelia
Complex or severe cases of meningomyelocele
Large encephaloceles
Acardia
Some cases of giant omphalocele
Inoperable conjoined twins
Cranioradischisis
Exencephaly
Iniencephaly
Harlequin fetus
Meckel–Gruber syndrome
Non-immune hydrops with major cardiac defects

Conditions are listed as cited, we do not necessarily endorse descriptions of these conditions as 'lethal'. This list does not include extreme prematurity (for example 22 weeks of gestation) severe oligohydramios/growth restriction or marked subcutaneous bullous cysts, although sometimes these conditions are grouped with LM, and similar issues apply to them.

paper quoted survival rates for these conditions, and since this publication survival until 13 months has been reported in a case of renal agenesis. Therefore counselling women whose pregnancy is complicated by a fetus with a severe abnormality is not a binary state of affairs but rather a complex discussion that requires a description of risk and probability.

Table 2. Published outcome for severe congenital anomalies frequently described as lethal

	Prevalence	Median survival	Proportion surviving >1 week	Longest reported survival
Renal agenesis	1.7/10 000[59]	<24 hours[59]	None reported	None reported
Anencephaly	10/10 000 pregnancies 2.6/10 000 births[60]	<24 hours[61,62] 55 minutes[63]	3–5%[61,64]	10 months,[65] 2.5 years[44]
Thanatophoric dysplasia	0.28/10 000[66]	Not reported	Not reported	5,[67] 9 years[68]
Trisomy 13	1.2/10 000[60]	7–8 days[29,30]	58%[69] 8% >1 year[29]	19,[72] 27 years[73]
Trisomy 18	2.6/10 000[60]	6–14 days[29,30]	52%[69] 8% >1 year[29]	27,[70] 30,[40] 50 years[71]
Holoprosencephaly	0.5/10 000[74]	4–5 months[31]	5/9 in series from Hungary[74]	6,[75] 11,[31] 13,[74] 19[76] years
Triploidy	1 in 10 000[77]	Not reported	Not reported	7 months[78]
Hydranencephaly	1–2.2/10 000[79]	1 month[79]	50%,[16] 15%, >1[79]	22,[80] 32 years[81]

Termination of pregnancy under clauses A and B

Whilst there is no gestational age limit set on termination of pregnancy under either of these two clauses, of the 250 cases in 2016, only 33 were performed after 20 weeks gestation, with a higher percentage of cases of clause A cases fulfilling this in comparison to clause B cases, where the risk is not to the life of the mother. In most cases once a certain gestation is reached and fetal survival is an option then delivery would no longer be a termination of pregnancy, but iatrogenic premature delivery.

Cases Studies

These cases are not actual cases but are representative of cases that we see.

1 Microcephaly

A woman who had a previously small baby had an uneventful pregnancy until 28 weeks gestation. She declined combined first trimester screening for trisomy 13, 18 and 21 and her scan at 20 weeks gestation was within normal limits. A scan performed to assess fetal growth at 28 weeks gestation showed that the fetal head circumference was small. Following referral to a fetal medicine centre these findings were confirmed and the fetal head circumference was 5.5 standard deviations below the mean for gestation. This is a very small head and although antenatal diagnosis of microcephaly is difficult, anything greater than 5 standard deviations below the mean is thought to be diagnostic. No other structural differences were seen in the baby and following counselling the couple opted for invasive prenatal diagnosis. An amniocentesis was performed and the results subsequently showed a normal fetal karyotype. At the time of the amniocentesis a plan was put in place to perform a fetal MRI and arrange an appointment with a paediatric neurologist if the chromosomes were normal. This plan was therefore enacted and when the couple were reviewed again at 31 weeks gestation the repeat ultrasound confirmed the previous findings. With this knowledge the couple requested termination of pregnancy and following an MDT two independent practitioners signed the HSA1 form, indicating that in good faith they were of the opinion that there was a substantial risk of significant handicap.

The couple therefore underwent a feticide and medical termination of pregnancy with a post mortem examination being performed. It is important to realise that microcephaly is rarely diagnosable before 24 weeks of gestation.

2 Selective Reduction

A woman presents at 11 weeks gestation and the ultrasound shows a monochorionic, diamniotic twin pregnancy. This is a pregnancy with two amniotic sacs but a single placenta. The twins are therefore 'identical' and their blood supplies are connected. One of the twins had anencephaly, a condition where the neural tube does not close at the cranial end and the brain tissue is gradually destroyed prior to birth. Although these babies may be able to breathe and suck following birth they only have primitive brain stem function and the

condition is generally considered a major abnormality. There is no inutero therapy for this condition and therefore the options are to continue with the pregnancy with all the risks that a monochorionic twin pregnancy has, terminate the whole pregnancy or to perform a selective reduction of the pregnancy coagulating the blood vessels in the affected fetus in order to separate the two circulations

In most multiple pregnancies where there is a structural difference present in one fetus the other will be discordant for this difference. Indeed only 18% of identical twins will have the same structural difference and the rate for dizygotic twins is similarly low. Therefore when a structural difference and abortion is the option chosen by the patient a selective termination of pregnancy is usually required. In this case the best chance of having a healthy live baby is to perform selective reduction.

Summary

Although termination of pregnancy is a common procedure in England and Wales only 2% are performed under clause E and in 2015 only 500 cases were performed under clause E after 22 weeks gestation. Termination of pregnancy in England and Wales is presented as one of the options available to women if their fetus is at substantial risk of significant handicap. Parliament has not defined either substantial or significant but have purposefully left it to the medical profession to make these decisions in good faith. Finally over 3000 women a year travel from the Republic of Ireland to England or Wales for a termination of pregnancy and in 2016, 141 of these had a termination of pregnancy under clause E of the Abortion Act.

References

1. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/652083/Abortion_stats_England_Wales_2016.pdf
2. https://www.rcog.org.uk/globalassets/documents/guidelines/terminationpregnancyreport18may2010.pdf
3. https://www.rcog.org.uk/globalassets/documents/guidelines/rcogfetalawarenesswpr0610.pdf
4. Wilkinson D, Thiele P, Watkins A, De Crespigny L. Fatally flawed? A review and ethical analysis of lethal congenital malformations. BJOG 2012;119:1302–1308