Institution: University College London / Birkbeck College

Unit of Assessment: 5 - Biological Sciences

Title of case study: The neurobiological basis of fetal awareness – impact upon recommended obstetric practice.

1. Summary of the impact

Research by Maria Fitzgerald's group in the Department of Neuroscience, Physiology & Pharmacology has provided fundamental biological knowledge of the development of pain pathways in the human fetus that is recognised all over the world. As a direct result of her published research, she co-authored a report from the Royal College of Obstetrics and Gynaecology on clinical recommendations for practice in fetal medicine and fetal termination. Published in March 2010, this report provides authoritative, evidence-based recommendations for medical practitioners, abortion advisory groups and patients, and consequently determines clinical practice throughout the UK. The recommendations impact upon a large number of women; in 2011 there were 196,082 abortions in England and Wales.

2. Underpinning research

The research underpinning this case report stems from Fitzgerald's studies of fetal and neonatal pain pathways which mapped the growth of nociceptive afferent terminals into the skin and into the central nervous system (CNS) before birth **[1]**. These data demonstrated that, while peripheral nociceptors develop prenatally, their central connections and thus their ability to transmit nociceptive information to the brain do not develop until just before birth **[2]**.

Subsequent research by Fitzgerald, on how pain pathways develop over the perinatal period, has elucidated the development of central signalling pathways, inhibitory circuits and descending brainstem control in the maturation of pain processing in early life **[e.g. 2,3]**.

At the same time, Fitzgerald has also pioneered the study of the neurobiology of infant human pain processing. In the human, the extremely premature infant is the closest model we have to the third trimester human fetus. Her early work in this area demonstrated that premature infants from 24 weeks gestational age (GA) can process nociceptive stimuli at spinal and brainstem level, but in a different way from older children and adults **[4]**. The research is notable for its use of quantitative neurophysiological techniques, grounded in basic neurobiology, to study CNS pain processing in very young preterm infants. This continues to the present day, using cot-side techniques such as near-infra red spectroscopy and electroencephalography (EEG) for direct brain measurement of pain processing in extremely preterm infants **[5]**.

Fitzgerald's work has clarified the difference between the onset of nociceptive reflex behaviour observed in fetal life, which requires intact circuits in the spinal cord and brainstem only, and the onset of pain 'awareness' or 'experience' which requires functional cortical connections. This is fundamental to the understanding of fetal pain. Recent work shows a transition in the premature infant brain response following tactile and noxious stimulation from nonspecific, evenly dispersed neuronal bursts to modality-specific, localised, evoked potentials between 24 weeks GA and term. The results suggest that specific neural circuits necessary for discrimination between touch and nociception emerge from 35-37 weeks gestation in the human brain **[5]**.

3. References to the research

[1] Jackman A, Fitzgerald M. The development of peripheral hindlimb and central spinal cord innervation by subpopulations of dorsal root ganglion cells in the embryonic rat. J Comp Neurol. 2000 Mar 13;418(3):281-98. http://dx.doi.org/10.1002/(SICI)1096-9861(20000313)418:3<281::AID-CNE4>3.0.CO;2-9

[2] Baccei ML, Fitzgerald M. Development of GABAergic and glycinergic transmission in the neonatal rat dorsal horn. J Neurosci. 2004 May 19;24(20):4749-57. http://dx.doi.org/10.1523/JNEUROSCI.5211-03.2004

[3] Hathway GJ, Koch S, Low L, Fitzgerald M. The changing balance of brainstem-spinal cord modulation of pain processing over the first weeks of rat postnatal life. J Physiol. 2009 Jun 15;587(Pt 12):2927-35. http://dx.doi.org/10.1113/jphysiol.2008.168013

[4] Andrews K, Fitzgerald M. The cutaneous withdrawal reflex in human neonates: sensitization, receptive fields, and the effects of contralateral stimulation. Pain. 1994 Jan;56(1):95-101. http://dx.doi.org/10.1016/0304-3959(94)90154-6

[5] Fabrizi L, Slater R, Worley A, Meek J, Boyd S, Olhede S, Fitzgerald M. A shift in sensory processing that enables the developing human brain to discriminate touch from pain. Curr Biol. 2011 Sep 27;21(18):1552-8. http://dx.doi.org/10.1016/j.cub.2011.08.010

MRC programme grant (Fitzgerald): Infant pain mechanisms – a short and long term view; Ref: G0400572; Jan 2005-Jan 2010; £1,086,101.

4. Details of the impact

Elective abortion is a matter of considerable political, social and ethical concern. The UK has one of the most liberal laws in the world, based upon scientific and clinical rationale and a strong sense of a woman's right to choose, rather than upon religious beliefs. After the introduction of The Abortion Act 1967, the Act of the United Kingdom Parliament legalising abortions by registered practitioners, and regulating the free provision of such medical practices through the National Health Service (NHS), the UK Government has regularly reviewed scientific evidence related to this Act.

As a direct result of her published research, Fitzgerald was asked to give evidence at a House of Commons Science and Technology Committee on the scientific evidence relating to the Abortion Act of 1967 **[a]**. This and other evidence from different sources led to the UK Government retaining the 24-week limit on abortion in the UK in 2007 **[b]**. This decision inevitably led to controversy, due to strong reactions from pro-life religious groups, many of whom are of the opinion that fetuses feel pain, are sentient and should not be terminated at any stage. The Minister of State for Health therefore commissioned the Royal College of Obstetrics and Gynaecology (RCOG) to review the scientific and clinical evidence for fetal awareness in detail and to update their original 1997 report on this subject (to which Fitzgerald had contributed) **[c]**. As a direct result of her published research on fetal nervous system development, and specifically the development of pain pathways, Fitzgerald was invited to join the working party and was a co-author of the updated, 2010 published report, entitled 'Fetal Awareness. Review of Research and Recommendations for Practice' **[d]**.

The intention of the report was to review the relevant science and clinical practice relevant to the issue of fetal awareness and, in particular, evidence published since 1997. In so doing, the report was completely rewritten to take account not only of recent literature but also of the evidence presented to the House of Commons Committee. The report concluded that, since most neuroscientists believe that the cortex is necessary for pain perception, it can be concluded that the fetus cannot experience pain in any sense prior to 24 weeks gestation. After 24 weeks there is continuing development and elaboration of intracortical networks such that noxious stimuli in newborn preterm infants produce cortical responses. Such connections to the cortex are necessary for pain experience but not sufficient, as experience of external stimuli requires consciousness. Furthermore, there is increasing evidence that the fetus never experiences a state of true wakefulness in utero and is kept, by the presence of its chemical environment, in a state of continuous sleep-like unconsciousness or sedation. This state can suppress higher cortical activation in the presence of intrusive external stimuli. The implications of these scientific observations for clinical practice are such that the need for analgesia prior to intrauterine intervention, for diagnostic or therapeutic reasons, becomes much less compelling. Indeed, in the

light of current evidence, the Working Party concluded that the use of analgesia provided no clear benefit to the fetus. Furthermore, because of possible risks and difficulties in administration, fetal analgesia should not be employed where the only consideration is concern about fetal awareness or pain **[e]**.

The number of women affected by this report is very high: in 2010, there were 189,574 abortions in England and Wales; in 2011 there were 196,082; in 2012 there were 185,122 **[f]**. Furthermore the impact spreads beyond the termination procedure itself to the long term physical and mental health of affected women. The RCOG's updated guidelines were followed by the Academy of Medical Royal Colleges' publication 'Induced abortion and mental health: a systematic review of the mental health impact of induced abortion' **[g]**. The purpose of the review was to examine the evidence of the impact of abortion upon women's mental health. The Academy's conclusions echoed the RCOG's guidelines.

This report has set the clinical and scientific standards for medical and allied health professions on the termination of pregnancy, and provided scientific underpinning for the current UK abortion law. It received considerable press attention with reaction from both pro-choice and pro-life groups **[h]** and the interest of medical ethicists **[i]**.

5. Sources to corroborate the impact

[a] House of Commons – Science and Technology Committee. Scientific Developments Relating to the Abortion Act 1967. HC 1045-I, Twelfth Report of Session 2006-07 – Volume I: Report, Together with Formal Minutes. TSO (The Stationery Office). http://www.publications.parliament.uk/pa/cm200607/cmselect/cmsctech/1045/1045i.pdf

[b] HM Government, Government response to the report from the House of Commons Science and Technology Committee on the Scientific Developments Relating to the Abortion Act 1967. http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_086538.pdf

[c] Royal College of Obstetricians and Gynaecologists. Fetal awareness: Report of a Working Party. London RCOG Press; 1997. Available on request.

[d] Royal College of Obstetricians and Gynaecologists. 'Fetal Awareness. Review of Research and Recommendations for Practice' . Report of a Working Party, March 2010. http://www.rcog.org.uk/fetal-awareness-review-research-and-recommendations-practice. Document: http://www.rcog.org.uk/files/rcog-corp/RCOGFetalAwarenessWPR0610.pdf

[e] RCOG clinical guidelines:
http://www.rcog.org.uk/womens-health/clinical-guidance/abortion-care
http://www.rcog.org.uk/termination-pregnancy-fetal-abnormality-england-scotland-and-wales
Document: http://www.rcog.org.uk/files/rcog-corp/TerminationPregnancyReport18May2010.pdf

[f] Abortion statistics for England and Wales:

- http://webarchive.nationalarchives.gov.uk/20130123231223/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_127202.pdf (2010)
- https://www.gov.uk/government/publications/report-on-abortion-statistics-in-england-and-wales-for-2011
- https://www.gov.uk/government/publications/report-on-abortion-statistics-in-england-and-wales-for-2012

[g] Wider impacts on women's mental health: Academy of Medical Royal Colleges report on 'Induced Abortion and Mental Health'. http://www.aomrc.org.uk/publications/reports-a-

guidance/doc_details/9432-induced-abortion-and-mental-health.html

[h] Examples of press reports: Telegraph and New Scientist, comments from pro-choice groups and pro-life groups:

- http://www.telegraph.co.uk/health/healthnews/7853321/Foetus-cannot-feel-pain-before-24-weeks.html This article generated 55 comments. Members of the general public debated the topic of abortion from both pro-life and pro-choice points of view.
- http://www.newscientist.com/article/dn19089-24week-fetuses-cannot-feel-pain.html
- http://www.prochoiceforum.org.uk/ocr_ethical_iss_4.php
- http://prolife.org.uk/2010/06/what-the-media-wont-tell-you-about-the-rcog-reports-on-fetal-pain-and-abnormality/
- http://www.salon.com/2013/08/07/fetal_pain_is_a_lie_how_phony_science_took_over_the_abortion_debate/. This article from Salon news website describes how the new laws that banned abortion after 20 weeks in many parts of the US are based on pseudoscience. The limited research used to support the idea that a fetus can experience pain at 20 weeks 'has been refuted by the Journal of the American Medical Association and by the British Royal College of Obstetricians and Gynaecologists'. Furthermore, the article states that 'the part of the brain that perceives pain is not connected to the part of the body that receives pain signals until about 26 weeks from the last menstrual period, which is about 24 weeks from conception.'

[i] Ethical study and RCOG ethical statement

- Strickland SL (2012) 'Conscientious objection in medical students: a questionnaire survey' J Med Ethics. 38(1):22-5. http://www.rcog.org.uk/what-we-do/campaigning-and-opinions/statement/rcog-statement-%E2%80%98doctors-anti-abortion-views-could-impa
- Article in The Guardian: http://www.theguardian.com/world/2011/jul/18/doctors-abortion-views