Institution: Ulster University

Unit of Assessment: Allied Health Professions, Dentistry, Nursing and Pharmacy (3)

Title of case study: ICS-9 Influencing regulatory and clinical guidelines on medication safety in pregnancy

Period when the underpinning research was undertaken: 2007 - 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Dr Maria Loane	Senior Research Fellow	2002 - present
Professor Helen Dolk	Professor of Epidemiology & Health Services Research	2000 - present
Dr Joanne Given	Research Fellow	2014 - present

Period when the claimed impact occurred: 2015 - 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Ulster University led research on the safety of medication use in early pregnancy which has had direct impact on the following areas:
I1 = An **EU-wide** regulatory decision requiring pharmaceutical companies to update patient information leaflets and add visible warnings to packaging of the antiepileptic drug sodium valproate so that women are informed of the risks to their unborn child when taking this medication in pregnancy.
I2 = **National** (NICE, UK) and **international** (WHO, US) guidelines which include our research on the safety of medications in pregnancy for women with depression, diabetes, and epilepsy.

2. Underpinning research

The need for research into medication safety in pregnancy
Major congenital anomalies are a leading cause of infant mortality, morbidity and long-term disability. Up to 80% of pregnant women in Europe are exposed to medication, yet only 5% of medication information leaflets include evidence on the safety of use in pregnancy, which highlights the importance of this area of research. Since 2005, Professor Dolk has led research on the risk of congenital anomalies associated with maternal medication exposure in the first trimester of pregnancy. In 2011, she established the EUROmediCAT network to conduct research studies into medication safety in pregnancy.

Dr Loane developed a European database to address hypotheses regarding teratogenicity i.e. risks of specific medications to the unborn child. This database, held at Ulster, holds data on approximately 281,200 congenital anomaly cases from 21 European registries including live births, fetal deaths from 20 weeks' gestational age and terminations of pregnancy for fetal anomaly.

Research into specific medications

Sodium valproate
Using our database, we performed a case-control study to investigate the risk of congenital anomalies associated with maternal exposure to the antiepileptic drug (AED) sodium valproate. We found a 13-fold increased risk of spina bifida and between 2-fold and 7-fold increased risks for five other congenital anomalies (heart, skull, limb, genital and cleft palate) associated with valproate exposure [**R1**].

We were part of a study to assess the impact of regulatory warnings issued in 2014 to restrict valproate prescribing in women and girls. The study assessed prescribing trends before and after these warnings and found that valproate prescriptions decreased by 23% in France, by 17-19% in Italy and by 8% in the UK after 2014 [**R2**].

Lamotrigine
We led a 5-year follow-up study to assess risks of orofacial clefts associated with maternal exposure to the AED lamotrigine [**R3**]. We found no evidence of increased risk of orofacial clefts associated with lamotrigine exposure in pregnancy, thus there was no evidence to support an earlier signal from a much smaller US study.

Antidepressants
We were the first research group to examine the full range of congenital anomalies associated with maternal exposure to antidepressants in a large European population. We found increased risks of heart defects, including severe heart defects, associated with exposure to antidepressants in pregnancy [**R4**]. Using a cohort study design in three countries, we found a 50% increased risk of severe heart defects associated with exposure to specific antidepressants [**R5**]. Underlying maternal depression or associated socioeconomic or lifestyle factors did not explain the excess risk. The high-quality congenital anomaly data makes these studies particularly important contributions to the evidence.

Diabetes medications
Our research on metformin [**R6**], a new approach to the treatment of women with diabetes during pregnancy, found no evidence of an increased risk of all major congenital anomalies combined. Our study had over five times the number of maternal metformin exposures compared to other studies in the literature, making it a particularly robust contribution to the evidence base.

Ulster obtained funding to conduct this research, see Section 3.

3. References to the research Outputs can be provided by Ulster University on request.

The following outputs have been published in international peer-reviewed journals:

R1 = Jentink J, **Loane MA, Dolk H**, Barisic I, Garne E, Morris JK, de Jong-van den LTW and the EUROCAT Antiepileptic Drug Working Group (2010). Valproic acid monotherapy in pregnancy and major congenital malformations. *New England Journal of Medicine* 362: 2185-2193

R2 = Charlton R, Damase-Michel C, Hurault-Delarue C, Gini R, **Loane M**, Pierini A, Puccini A, Neville A, Snowball J, Morris JK, on behalf of the EUROmediSAFE consortium (2019). Did advice on the prescription of Sodium Valproate reduce prescriptions to women? An observational study in three European countries between 2007 and 2016. *Pharmacoepidemiology and Drug Safety* 28(11): 1519-1528

R3 = **Dolk H**, Wang H, **Loane M**, Morris J, Garne E, Addor MC, Arriola L, Bakker M, Barisic I, Doray B, Gatt M, Kallen K, Khoshnood B, Klungsoyr K, Lahesmaa-Korpinen AM, Latos-Bielenska A, Mejnartowicz JP, Nelen V, Neville A, O'Mahony M, Pierini A, Rißmann A, Tucker D, Wellesley D, Wiesel A, and de Jong-van den Berg LTW (2016). Lamotrigine use in pregnancy and risk of orofacial cleft and other congenital anomalies. *Neurology* 86 (18): *1716-25*

R4 = **Wemakor A, Casson K**, Garne E, Bakker M, Addor M-C, Arriola L, Gatt M, Khoshnood B, Klungsoyr K, Nelen V, O'Mahony M, Pierini A, Rissmann A, Tucker D, Boyle B, de Jong-van den Berg L, **Dolk H** (2015). Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: A European register-based study. *Eur J Epidemiol* 30(11):1187-1198 (DOI: 10.1007/s10654-015-0065-y)

R5 = Jordan S, Morris JK, Davies GI, Tucker D, Thayer DS, Luteijn JM, Morgan M, Garne E, Hansen AV, Klungsøyr K, Engeland A, Boyle B, **Dolk H** (2016). Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants in Pregnancy and Congenital Anomalies: Analysis of Linked Databases in Wales, Norway and Funen, Denmark. *PLoS ONE* 11(12): e0165122. https://doi.org/10.1371/journal.pone.0165122

R6 = **Given JE, Loane M**, Garne E, Addor MC, Bakker M, Bertaut-Nativel B, Gatt M, Klungsoyr K, Lelong N, Morgan M, Neville AJ, Pierini A, Rissmann A, **Dolk H** (2018). Metformin exposure in first trimester of pregnancy and risk of all or specific congenital anomalies: exploratory case-control study. *BMJ* 361: k2477.

Title	Funder	Researcher	Amount	Date
EUROCAT (European Surveillance of Congenital Anomalies)	EU Public Health Programme 2004-2014 (4 contracts)	Prof H Dolk (PI), Dr M Loane (CI)	GBP5,500,000 Ulster apportionment: (i) EUR1,471,299 (ii) EUR629,549 (iii) EUR1,106,302 (iv) EUR316,630	2004 - 2014
EUROmediCAT: Safety of medication use in relation to risk of congenital anomaly	EU Framework 7	Prof H Dolk (PI), Dr M Loane (CI) Prof M Sinclair (CI)	EUR2,996,100 Ulster apportionment: EUR1,023,793	2011 - 2015
EUROmediSAFE	European Medicines Agency	Prof H Dolk (CI), Dr M Loane (CI)	EUR229,150 Ulster apportionment: GBP8,646	2017 - 2018
A case control study of isolated orofacial clefts and in utero exposure to lamotrigine	GlaxoSmithKline Research & Development Ltd	Prof H Dolk (PI), Dr M Loane (CI)	GBP451,250	2009 - 2013

4. Details of the impact

Our research had the following impact:

I1: EU-wide regulatory decision requiring pharmaceutical companies to update patient information leaflets and add warnings of risks in pregnancy to packaging of the AED sodium valproate.

In 2016, the French medicines regulator cited our sodium valproate study [**R1**] as evidence for increased risk of congenital anomalies associated with exposure during pregnancy [**C1**]. The regulator presented this evidence at the European Medicine Agency (EMA) to highlight its concerns about the effectiveness of measures to increase awareness and reduce valproate exposure in females. Despite the warning to restrict valproate prescribing in women of childbearing age implemented in November 2014, studies reported that valproate was still being prescribed to these women.

In response to these concerns, the EMA published further official guidance in 2018 banning the use of valproate for migraine or bipolar disorder during pregnancy, or for the treatment of epilepsy during pregnancy unless no other effective treatment was available [**C2**]. In addition, pharmaceutical companies were instructed to add visual warnings of the risks in pregnancy to the packaging of valproate medicines and to update the medicine information leaflet to ensure the risks during pregnancy are clearly stated [**C2, C3**].

In 2018, Ulster was part of a consortium commissioned by the EMA to assess valproate prescribing trends in women and girls in relation to its 2014 warnings. We found that valproate continued to be prescribed in women aged between 10-50 years in the UK, Italy and France [**R2**].

This illustrates the reach and significance of the impact arising from our research as it led to EU-wide regulatory changes to highlight the warnings of risk of valproate exposure during pregnancy. Our research directly informed the EMA regulatory body that valproate continued to be prescribed to women of childbearing age in Europe.

I2 = National (NICE, UK) and international guidelines (WHO, US) include our research on safety of medications for pregnant women with depression, diabetes and epilepsy.

National: Our research assessing the safety of AEDs [**R1**] has been included in NICE national guidelines on antenatal and postnatal mental health (2015) and has been used to build a body of evidence to guide and inform decision-making for the safe and effective use of AEDs during pregnancy [**C4**]. In England, NICE reviewed the impact of the regulatory guidelines on valproate prescribing in women of childbearing age and reported that the number of females receiving a prescription for sodium valproate steadily decreased from 23,935 in early 2016 to 13,251 in the summer of 2020 [**C5**]. This is evidence that clinical practice in relation to valproate prescribing in women of childbearing age is changing.

In 2017, the British Association for Psychopharmacology, which is the largest such national association in Europe, cited our research on the safety of valproate [**R1]** and lamotrigine [**R3]** in pregnancy in their consensus guidance on the use of psychotropic medication in pregnancy [**C6**].

In 2018, our research on the safety of selective serotonin reuptake inhibitor antidepressants in pregnancy [**R5**] was cited in The Maudsley Prescribing Guidelines in Psychiatry [**C7**]. This textbook is an established reference source for ensuring the safe and effective use of medications for patients presenting with mental health issues.

The UK Teratology Information Service provides online monographs for health care professionals summarising key research studies that have investigated the effects of prenatal medication exposures on the fetus [**C8**]. The “Selective Serotonin Re-uptake Inhibitors (SSRIs) in Pregnancy” monograph, issued in 2017, included our research on antidepressant use in pregnancy [**R4, R5**].

International: In 2017, following a review of the literature on the safety of medications which included our research [**R3]**, lamotrigine was added to the list of essential medicines recommended by the World Health Organisation Expert Committee on the Selection and Use of Essential Medicines [**C9**].

In 2018, our research [**R6**] on the safety of metformin in pregnancy and risk of congenital anomalies was cited in the American College of Obstetricians and Gynecologists Practice Bulletin [**C10**]. This Practice Bulletin provides current evidence-based information on the clinical management of pregnant women with pregestational diabetes.

In summary, there is national and international evidence of the reach and significance of our research as it is cited in current clinical guidance on the management of women with diabetes, depression and epilepsy in pregnancy [**C4, C6-C10**]. The impact of our research benefits health care providers who wish to provide optimal treatment to pregnant women while decreasing potential risks that the medication may pose to the fetus. It also benefits pregnant women who have access to more evidence about medication safety in pregnancy.

5. Sources to corroborate the impact

C1 = Enquête relative aux spécialités pharmaceutiques contenant du valproate de sodium. Février 2016, Inspection générale des affaires sociales (IGAS) Rapport No 2015-094R. Page 121. French language item.

C2 = European Medicines Agency report (2018).

C3 = Sodium Valproate patient information leaflet.

C4 = National Institute for Health and Care Excellence (2015). "Antenatal and postnatal mental health. Clinical management and service guidance". Updated edition. National Clinical Guideline Number 192. Pages 734, 746.

C5 = National Institute for Health and Care Excellence "Spotlight on valproate prescribing", which is part of the NICE Impact Report on Maternal and Neonatal Care (Sept 2019). Page 16. Associated NHS Business Services Authority sodium valproate prescribing data up to July-September 2020.

C6 = British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017: Journal of Psychopharmacology 2017. Volume: 31, Issue: 5. Page 536.

C7 = "The Maudsley Prescribing Guidelines in Psychiatry", 2018. 13th Edition, Wiley Blackwell, Oxford. Page 606.

C8 = UK Teratology Information Service Monographs (available in TOXBASE) for use by heath care professionals. Our research is cited in the "Selective Serotonin Re-uptake Inhibitors (SSRIs) in Pregnancy" monograph, issued in 2017 (p5).

C9 = Report of the WHO Expert Committee, 2017 "The Selection and Use of Essential Medicines". (WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development). Page 50.

C10 = American College of Obstetricians and Gynecologists Practice Bulletin No. 201 (2018); VOL. 132, NO. 6. Pregestational Diabetes Mellitus (Page e236).