Pregnancy Sickness Support,
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12rd September 2019

Dear Dr Straus and PRAC members,

RE: EMA/PRAC/347675/2019

We are writing to you as a group of charities, clinicians, researchers and advocates working to support women suffering from hyperemesis gravidarum (HG). We are deeply concerned about the recent adoption of a Pharmacovigilance Risk Assessment Committee (PRAC) recommendation Adopted at the 8-11 July 2019 PRAC meeting stating that ondansetron should not be used during the first trimester of pregnancy, and urge that this decision be reconsidered.

The burden of HG

When indicated for hyperemesis gravidarum, ondansetron is one of our few effective treatments, and for some people could be considered a life-saving treatment. Women requiring ondansetron in the first trimester are generally very unwell, malnourished, and dehydrated from their nausea and vomiting symptoms.

The physical complications from HG present serious risks such as Wernicke's encephalopathy (1) and cardiac arrest (2). Other complications caused by the poor management of HG include oesophageal tears, pressure sores and deep vein thrombosis (3). Even now, it is not unheard of for women to die from HG (4). Furthermore, the risks associated with malnutrition in early pregnancy, such as cardio-metabolic disorders in the offspring, are well established (5). The impact on a woman's mental health caused by their immense suffering can be just as profound. Women can suffer poor mental health and become suicidal from the severity of their symptoms and the battle they face to obtain appropriate treatment (6-8).

The burden of both the physical and mental symptoms of poorly managed HG can force women to make the agonising decision to end a much-wanted pregnancy. The termination rate of otherwise healthy, wanted pregnancies for HG has been estimated to be between 5-20% (9, 10). These women report grief, sadness, and regret, not for the abortion itself but regarding the circumstances that led to it (9).

Current treatment options for HG are limited and ondansetron is an important medication in the management of symptoms. To deny women the option of ondansetron will result in a vast increase in maternal morbidity, an increase in the termination of wanted pregnancies, and a potential increase in maternal mortality (11).

The evidence base

The document detailing PRAC recommendations on signals adopted at the 8-11 July 2019 PRAC meeting states that:

"Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48))."

The paper by Huybrechts, Hernández-Díaz (12) on which PRAC'S recommendation is based shows a very small absolute increased risk of oral clefts in babies born to women who used ondansetron in the first trimester of pregnancy (an additional 3 per 10,000 live births). The epidemiological evidence points to a potential association, not a causal relationship between ondansetron and orofacial malformations. Additionally, confounders such as HG associated micronutrient deficiency, particularly folate deficiency, which is also associated with oral clefts, cannot be ruled out. Moreover, when these findings are considered in conjunction with other literature the picture is less clear. A previous systematic review on birth defects and ondansetron in early pregnancy, came to the conclusion that *"…thorough search of the literature and rigorous independent review of all data on ondansetron use in pregnancy and the risk of congenital malformations did not yield significant safety concerns".* (13)

The very small increased risk of a fetus developing a cleft lip must be balanced against the very real suffering of women with HG (which can be a life and death situation), the aforementioned potential long term health consequences for pregnant women with HG, as well as the risks associated with malnutrition and dehydration for the developing fetus.

What are we asking for?

Women already face a battle for treatment of HG. The recommendation that ondansetron must not be used in the first trimester due to a very small *possible* increased risk of oral cleft will have dire real-world consequences. The benefits of ondansetron in preventing maternal morbidity and mortality, and the termination of wanted pregnancies must be recognised and the risks weighed against the benefits. It is likely that these recommendations will also limit ondansetron access for women beyond the first trimester and cause unnecessary fear for its use in women of childbearing age.

We would urge you not just to consider changing the recent PRAC recommendations as a matter of urgency, but to also engage on a wider scale with women affected by HG and nausea and vomiting in pregnancy who need to take medication, and the experts who prescribe it.

Specifically, we request that the advice be changed to "*women must be counselled about the risks and benefits of taking ondansetron in order to make an informed decision*".

I look forward to hearing from you on this urgent matter soon

Yours Sincerely,

Caitlin Dean, Signed on behalf of Pregnancy Sickness Support, British Pregnancy Advisory Service and the below registered charitable patient organisations and signatories

Organisations:

- Hyperemesis Ireland, Ireland
- Stichting ZEHG, The Netherlands
- Hyperemesis Gravidarum Norge, Norway
- HG Danmark, Denmark
- Hyperemesis Gravidarum Sverge, Sweden
- Association de lutte contre l'hyperémèse gravidique, France
- Hyperemesis NETZ, Germany
- Birthrights, UK
- WRISK Project, UK

Signatories:

- Professor Catherine Nelson-Piercy, Professor of obstetric medicine and consultant obstetric physician, Guy's & St Thomas' Hospital, London UK
- Dr Rebecca Painter, Rebecca C. Painter, MD PhD, Consultant Obstetrician, Associate Professor, Department of Obstetrics and Gynaecology, Academic Medical Centre, Amsterdam
- Dr Krista F. Huybrechts, MS PhD, Associate Professor of Medicine, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02120
- Dr Brian Bateman Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts
- Dr Ken Hodson MD MRCP(UK) MRCOG, Head of UK Teratology Information Service (UKTIS: www.uktis.org), Consultant in Obstetrics and Maternal Medicine, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP
- Dr. Manjeet Shehmar, MMedEd, MRCOG, BSc, Consultant in Obstetrics & Gynaecology, Birmingham Women's Hospital
- Prof Catherine Williamson, Professor of Women's Health, Kings College, London, UK
- Dr Aldo Maina, Dipartimento di Ostetricia e Neonatologia, Servizio di Medicina Interna, Ospedale Sant'Anna, corso Spezia 60, Torino 10126, Italy
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- Hanne Brix Westergaard, President of the Danish Society of Obstetrics and Gynaecology, Associate professor, Consultant, MD, PhD , Dept. of Gynaecology and Obstetrics, North Zealand Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark
- Tonny Studsgaard Petersen,Associate Professor, Consultant, MD, PhD, Dept. of Clinical Pharmacology, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark
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- Anne Ostenfeld, MD, PhD student, Dept. of Gynaecology and Obstetrics, North Zealand Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark
- Dr Jone Trovik, Department of Clinical Science, University of Bergen, Bergen, Norway, Department Obstetrics and Gynaecology, Haukeland University Hospital, Jonas Liesvei 72, 5021, Bergen, Norway

- Dr Brian Cleary, Chief Pharmacist, Rotunda Hospital, Honorary Clinical Associate Professor, RCSI.
- Clare Murphy, British Pregnancy Advisory Service, 30-31 Furnival St, Holborn, London EC4A 1JQ

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