Modafinil and the risk of congenital malformations: Implications for practice

There is evidence that the undisclosed use of modafinil as a 'smart drug' is increasing. Modafinil may reduce the effectiveness of steroidal contraception, including oral contraceptives. Modafinil may increase the risk of congenital malformations when used in pregnancy.

Key message for women: Modafinil may reduce the effectiveness of contraception agents. Tell your doctor or pharmacist if you are taking modafinil, whether it is prescribed for you or not.

Key message for healthcare professionals: Modafinil may reduce the effectiveness of standard contraception regimens. Consider the potential for undisclosed modafinil use when prescribing or dispensing contraception. Women should use effective contraception while using modafinil, and for 2 months after stopping.

Background:

Modafinil is used for a number of licensed and unlicensed indications, including the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy[1], fatigue related to multiple sclerosis and for the treatment of attention-deficit/hyperactivity disorder. There are also reports of modafinil being used as a "smart drug" to increase concentration and overall cognitive performance[2,3]. **There is evolving evidence that modafinil use during pregnancy may be associated with an increased risk of major congenital malformations (MCM).**

Evidence of major congenital malformation:

In 2019, following a review of data ascertained from a modafinil pregnancy registry in the United States, the marketing authorisation holders (MAH) of products containing modafinil, in agreement with the European Medicines Agency (EMA) and Health Product Regulatory Authority (HPRA), issued new safety information regarding the potential association between modafinil use during pregnancy and the risk of MCM.[4] An interim analysis of post marketing surveillance data suggested that the rate of MCM was approximately 15% compared with 3% in the general population[4]. A recent update from this registry, including cumulative data up to February 2019, substantiated the reported increase in MCM rate among modafinil exposed pregnancies (13%)[5].

Two epidemiological studies have subsequently been published on the risk of MCM with modafinil. The first, by Broe and Damkier[6], used the Danish Medical Birth Register and reported a major malformation rate of 12% (n= 6/49) among modafinil exposed pregnancies, compared with 3.9% (n= 32 466/828,644) in un-exposed pregnancies. This represents a three-fold increase in the risk of MCM in pregnancies exposed to modafinil in the first trimester (adjusted Odds Ratio 2.7 (95% CI, 1.1-6.9) when compared with unexposed pregnancies[6] and is consistent with data reported from the modafinil pregnancy registry[5]. The second study by Cesta et al.[7] used data from the Norwegian and Swedish Medical Birth Registers and reported a major malformation rate of 2.6% (n =3/133) among modafinil exposed pregnancies, compared with 2.1% (n = 40,697/1,917,472) in un-exposed pregnancies. The authors reported that modafinil use during early pregnancy was not significantly associated with increased risk of major malformations (RR 1.06 (95%CI 0.35-3.26). Despite this, the authors

note the overlapping 95% CIs estimated in the Danish study allow for the possibility of a greater than 3-fold risk as previously reported[7].

Because no specific organ malformation pattern has been identified, a clear causal association between use of modafinil and MCM cannot be established[7]. Until further data are available, care is advised if modafinil is used in women of child bearing potential.

IMPS Response:

The Irish Medicines in Pregnancy Service (IMPS) wishes to highlight the potential risk of congenital malformations with modafinil in the context of:

1. The potential for undisclosed use of modafinil as a study aide or 'smart-drug'
2. The potential interaction between modafinil and steroidal hormonal contraception

1. Potential for undisclosed use of modafinil as a study aide

Recent reports suggest illicit and off-label use of modafinil as a 'smart-drug', in an effort to enhance cognitive performance, especially during exam periods. This suggestion is supported in the Irish context through reports from the HPRA of increased modafinil detections between 2016 and 2021[8] (Figure 1). IMPS wishes to highlight the potential risk of major congenital malformations in the context of undisclosed modafinil use by women seeking hormonal contraception or emergency contraception.

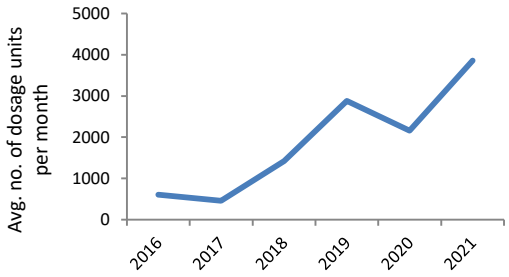

Figure 1: Average number of modafinil dosage units detained per month - reported by the HPRA (2016-2021)

IMPS advocates for an educational campaign directed at students and smart-drug users highlighting:

- Importance of effective contraceptive methods if using modafinil to enhance cognitive performance.
- Potential impact of modafinil on hormonal contraception and recommendation for consistent and careful use of condoms even if taking other hormonal contraception.
- Potential impact of undisclosed modafinil use on the efficacy of emergency contraception and potential for contraceptive failure and unplanned pregnancy.

2. Potential interaction with modafinil and hormonal contraception

Modafinil is an enzyme-inducer and has potential interactions with hormonal contraceptives and emergency contraceptives. In the context of a potential association between modafinil and MCM, IMPS provides the following recommendations:

- Healthcare providers should ensure women who are using modafinil are prescribed effective hormonal contraception[2]:
  - Long acting reversible contraceptives including depo-medroxyprogesterone acetate (Depo-provera®), levonorgestrel-releasing intrauterine device or copper intrauterine device are preferred[2].
  - Combined hormonal contraceptive, progestogen-only pill and progestogen-only implant should not routinely be used. The Faculty of Sexual and Reproductive Healthcare (FSRH) provides specific advice on the use of oral contraceptives regimens where a woman specifically chooses a combined hormonal contraceptive[2].
  - In cases of short-term use of enzyme-inducing drugs (<2 months) FSHR advises that continuing the contraception method with consistent and careful use of condoms may be appropriate[2].
- Women using enzyme-inducing drugs, such as modafinil, who require emergency contraception should be offered a Copper intrauterine device (Cu-IUD). If a Cu-IUD is unacceptable or unsuitable, a double dose of levonorgestrel emergency contraception may be used[2]. Ulipristal acetate should not be used as emergency contraceptive in women taking modafinil[2].

References:

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8. Personal communication with Health Products Regulatory Authrority (Sept 2021)

Modafinil unexposed pregnancy

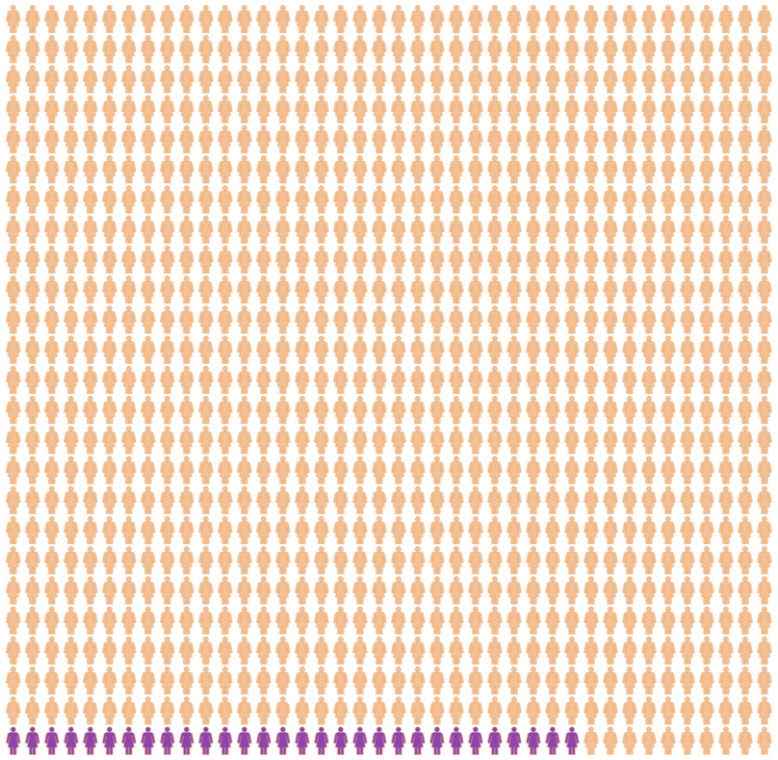

Figure 2. Rate of major congenital malformations in modafinil non-exposed pregnancies- 30 per 1,000[4]

Modafinil exposed pregnancy

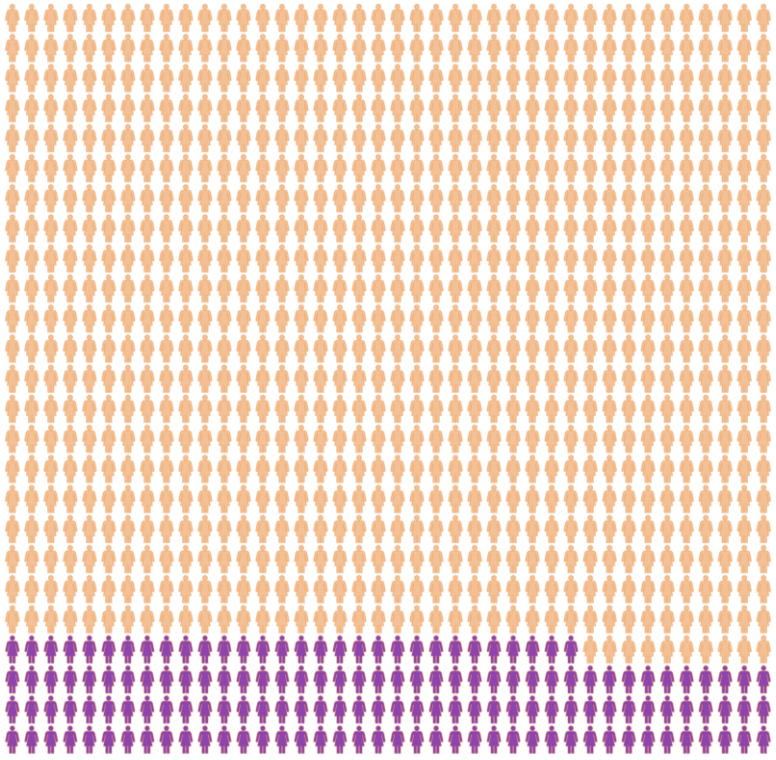

Figure 3. Rate of major congenital malformations in modafinil exposed pregnancies- 150 per 1,000[4]

About the Irish Medicines in Pregnancy Service

Established in 2019, the Irish Medicines in Pregnancy Service (IMPS) is a multidisciplinary team that aims to support safe and effective medication use in pregnancy through clear, evidence-based risk communication. IMPS is based at the Rotunda Hospital, Dublin, and is an associate member of the European Network of Teratology Information Services (ENTIS).