

Hormonal contraception and suicide:

a new dimension of risk

GENDER AND MENTAL HEALTH

Women have a higher lifetime prevalence of mood or anxiety disorders than men,^{1,2} with sex and gender differences within psychiatric diagnoses and course of psychiatric illness more broadly well documented.³

In a recent review, Christine Kuehner identified a wide range of potential reasons for this sex divide.⁴ These included; the influence of sex hormones; women's blunted hypothalamic-pituitary-adrenal axis response to stress; girls' and women's lower self-esteem and higher tendency for body shame and rumination; higher rates of interpersonal stressors; and experience of violence, and childhood sexual abuse.⁴ With such a broad range of potential implicating risk factors, there has been a drive for research to focus and analyse some of these areas.

HORMONAL CONTRACEPTION & SUICIDE

In a recent study in the *American Journal of Psychiatry*, Skovlund and colleagues provide an elegant and eye-opening report of their finding that hormonal contraception use doubles the risk of suicide attempt, and triples the risk of suicide.⁵

The study utilised a nationwide registry in Denmark to identify 475 802 women, with a mean follow-up of 8.3 years: 54% of the cohort used hormonal contraception at some point during the study period. Patients with a known history of psychiatric diagnoses, including previous suicide attempts or prescription of antidepressants, were excluded from analysis, and patients were censored temporarily during pregnancy and 6 months after delivery to reduce the influence of postpartum depression. The outcome measure was death by suicide, and a diagnosis and/or contact with healthcare provider with 'suicide attempt' coding.

The authors reported that adolescent women are more sensitive than older women to the influence of hormonal contraception on first suicide attempt. In terms of dose-response effects, the risk of suicidal behaviour tended to be higher in women who received 50 µg compared to those who received 20–40 µg of ethinyl estradiol, and higher in those who used progesterone-only contraception. Non-oral hormonal contraception conferred the highest risk.

The association between hormonal contraception and primary outcomes peaked

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at 2 months, but continued even after the cessation of hormonal contraception for some years.

The strengths of this study are similar to other large-scale registry-based analyses: a large and representative sample; a long prospective follow-up; and careful methodology. Indeed, alongside censoring pregnancy, the authors differentiated between current and past use of hormonal contraception and reported effects by type of contraception. The study was able to clearly demonstrate that hormonal contraception preceded suicidal behaviour.

Limitations included a lack of information with regards to the risk factors that may well be influential in the relationship between hormonal contraception and suicidal behaviour. These include important social factors, such as relationship break-down/status, exposure to domestic abuse, and strong family history of mental health diagnoses. Being able to combine such data would be of particular relevance for primary care, where decisions about contraception are often made with information about the patients broader context more likely to be known than secondary care. The selection of comparison groups could have been associated with bias. With a younger age group hormonal versus non-hormonal forms of contraception may have been more valid. It could be postulated that earlier sexual encounter and risky sexual behaviour could be associated with suicidal behaviour. Finally, in the UK patients can be diagnosed with postnatal depression up until 12 months after delivery rather than the 6 months used as a censor in this study.

A PLAUSIBLE RELATIONSHIP BETWEEN HORMONES AND SUICIDE

The relationship between hormonal contraception exposure and suicidal behaviour is plausible for several reasons.⁶ Previous work by Skovlund and colleagues⁷ reported an association between hormonal contraception and depression (a 70% higher risk of depression among users of hormonal contraception compared to non-users), and indeed in clinical practice mood symptoms are a common reason for patients to cease hormonal contraception or change to a different preparation. A double-blind, placebo-controlled trial looking at the sex hormone manipulation with goserelin (a gonadotropin-releasing hormone agonist) found that women receiving goserelin experienced subclinical depressive symptoms, and these symptoms were positively associated with an overall decrease in estradiol levels.⁸ The study also reported cerebral changes on positron emission tomography.⁸ There have been other neuroimaging studies which have shown alterations in brain structure and functioning associated with contraceptive use.^{6,9} However, a recent randomised study which assigned women with a history of depression in the follicular phase of the menstrual cycle, to receive 30 µg of ethinyl estradiol/0.15 mg levonorgestrel or placebo, did not find an association between alterations in brain functioning and depressive symptoms.¹⁰

PLACING RESEARCH IN CONTEXT

How should this study begin to influence clinical practice? The first thing to stress is

"... it would be prudent for GPs to consider mental health risk factors when starting and reviewing hormonal contraception ..."

that women on hormonal contraception, of all forms, should not stop using them. The improvement in the provision of sexual health and contraceptive options for women has been a key development over the past 20 years, and it is important not to use this data to lead to hesitancy in prescribing contraception to patients. Indeed, the most recent MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) report looking at maternal deaths between 2013 and 2015 found that maternal suicide is the third largest cause of direct maternal deaths occurring during or within 42 days of the end of pregnancy.¹¹ Furthermore, suicide remains the leading cause of direct deaths occurring during pregnancy, or up to a year after pregnancy.¹¹

The relationship between unintended pregnancy and abortion on mental health outcomes is not clear. There had been concerns following a review that reported higher risk of mental health conditions after an abortion.¹² However, numerous flaws and methodological issues were reported and discussed at length^{13,14} and there is no clear consensus on this issue presently, with longitudinal research on this issue planned.

However, it can be now argued that we should be counselling patients regarding mood side effects with hormonal contraception, with the caveat that the

study effect for the individual will be small. This can provide the basis for a patient-healthcare professional discussion, with patients encouraged to highlight concerns in their mood fluctuations after starting treatment to their clinician.

Further work is needed to try and further decipher the relationship between hormones and mental health, and how known social risk factors for affective disorders may interact with hormonal fluctuations and hormonal treatment. Based on the results of the study by Skovlund and colleagues, it would be prudent for GPs to consider mental health risk factors when starting and reviewing hormonal contraception in the management and treatment of female patients in the community.

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