

Hormonal contraceptive use and risk of attempted and completed suicide: a systematic review and narrative synthesis

Abstract

Background: Despite its widespread use, there is conflicting evidence on the association between hormonal contraception and the risk of suicide among women. This review seeks to identify, appraise and synthesize all studies on the association between hormonal contraceptive use and attempted or completed suicide.

Methods: A systematic review was performed in accordance with PRISMA guidelines. Relevant citations were identified from three bibliographic databases (MEDLINE, EMBASE, and PsycInfo). Cross-sectional, cohort and case control studies were included. Quality of studies was assessed with validated tools, and a narrative synthesis was conducted to summarize study findings.

Results: Nine studies reporting on six samples ($n=683,198$) were included. Three studies reported data for the association between hormonal contraceptive use and suicide attempts, and five studies reported data on completed suicides. Both protective and adverse associations between hormonal contraception and risk of suicide were identified. The evidence of the association was weakened by low to moderate methodological quality of studies.

Conclusion: Our review found there was substantial variability in the relationships reported between hormonal contraceptive use and suicide risk. Going forward, researchers investigating this topic are encouraged to use population-based samples to take efforts to control for important confounding variables. Additional research is also needed to investigate the effects of more recent hormonal contraceptive methods on suicide risk.

Key Words: hormonal contraception; oral contraceptives; suicide; suicide attempt; systematic review

Background

Today, more than 100 million women worldwide use hormonal contraception [1]. Since their introduction more than fifty years ago [1], hormonal contraceptives have provided women with an opportunity to exercise control over their health and well-being by avoiding unintended pregnancies [2]. Hormonal contraceptives relieve menstrual cramps, heavy bleeding, endometriosis, acne, and protect against ovarian and endometrial cancers [2, 3]. There are both benefits and risks involved with hormonal contraceptive use. Studies have detected an increased risk of venous thromboembolism [4], cardiovascular events such as myocardial infarctions [4] and breast cancer [5] among hormonal contraceptive users, although there is some uncertainty about the validity of these findings [2]. There are several different types of hormonal contraceptives with varied methods of administration including the pill, the vaginal ring, implantable rod, short/injection as well as different profiles of associated benefits and risks [3]. These are outlined further in Appendix 1.

Despite its widespread use, the literature surrounding hormonal contraceptives' neural and psychological effects is unclear. While some studies have associated hormonal contraception with risk of depression [6], others have found them to be protective against adverse mood events [7]. There is evidence to suggest that periods of hormonal fluctuation or transition such as puberty and menopause are linked to increased risk of depressive episodes in women [8,9]. However, the impact of exogenous hormones on these fluctuations and its corresponding psychological effects have been less studied. A recent large study has suggested an association between hormonal contraception and increased risk of suicide [10], but other studies show inconsistent results [11] and there have been no published systematic reviews to date.

Given that suicide is one of the leading global causes of death among women of reproductive age [12], a systematic review on the association between hormonal contraceptive use and attempted and completed suicide is warranted. The objective of this paper is to (1) to report the effect sizes on the association between hormonal contraceptive use and attempted and completed suicides, (2) critically appraise the methodology of studies to assess the quality of evidence and (3) synthesize the evidence on the association between hormonal contraceptive use and suicide risk and provide recommendations for future research on this topic.

Methods

The review was registered with PROSPERO (Registration No. CRD42019134087) and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Appendix 2) [13]. Peer-reviewed cross-sectional, cohort and case control studies were included if they reported data on attempted or completed suicide in women taking any form of hormonal contraception and used an appropriate control group. Attempted suicide was defined as a “non-fatal self-directed potentially injurious behavior with any intent to die as a result of the behavior” [14] whereas suicide was defined as “death caused by self-directed injurious behavior with any intent to die as a result of the behavior” [14]. Study inclusion and exclusion criteria are further presented in Appendix 3. The search strategy, developed in collaboration with librarians combined search terms for different types of hormonal contraception with search terms for suicide (full search strategy presented in Appendix 4). Three bibliographic databases (MEDLINE, EMBASE and PsycINFO) were searched from inception to May 2020. Forward and backward citation tracking of eligible papers was conducted. Two authors independently screened for relevant titles and abstracts and subsequently reviewed full text to determine final inclusion.

Data on study characteristics, type of hormonal contraceptive used, comparator group, outcome measures and effect sizes was extracted. Studies were independently assessed for risk of bias using checklists provided by the Joanna Briggs Institute (JBI) [15] by two authors and conflicts were resolved through discussion with a third author. Overall ratings were assigned to individual studies based on criteria adapted from Lund et al (2010) [16]. A narrative synthesis was carried out in accordance with the recommendations provided by Popay et al [17]. Where sufficient data were presented in the individual studies, we examined study findings by type and duration of hormonal contraception use, mental health history and participants age.

Results

The literature search strategy identified a total of 1,728 records and three more were identified through backward and forward citation tracking. Following de-duplication, 1,132 titles and abstracts were screened for inclusion; of these, sixteen articles were identified for full text review. Full-text articles were excluded if they did not report on the outcomes of interest (n=2), exposure data were not available separately for hormonal and non-hormonal contraceptive methods (n=3), or were qualitative in nature (n=2). Ultimately, nine articles met the pre-specified inclusion criteria

(see Figure 1).

<< Place Figure 1 about here >>

The nine included studies reported on six different samples: two papers reported different follow-up periods of the Oxford Family Planning Association Study [18,19], two reported different follow-up periods for the Royal College of General Practitioners' Oral Contraception Study [11, 20] and two other reported different follow-up periods for The Nurses' Health Study [21, 22]. Two populations were from the UK [11,19], two were from the US [22, 23] one was from Denmark [10] and one consisted of women from Bangladesh, Chile, China, Colombia, Egypt, Indonesia, Sri Lanka and Thailand [24]. Oral contraception (OCP) was the form of hormonal contraception used by women in three of the six populations (n=184,721) [11,19, 22], women in two studies used a variety of different hormonal contraceptives such as the OCP, patch or vaginal ring (n=482,456) [10,23] and women in one study used the Norplant contraceptive implant exclusively (n=16,021) [24]. Comparators used included women using non-hormonal forms of contraception [19, 23, 24] or women who had never used hormonal contraceptives [10, 20, 22]. Only one study [23] included depressive symptoms as a covariate. Whereas other excluded women with a history of antidepressant use or known psychiatric diagnoses from its study population [10]. An summary of individual studies is provided in Table 1.

<< Place Table 1 about here >>

Association between hormonal contraceptive use and attempted suicides

Overall, three studies of three unique samples presented data for an association between hormonal contraceptive use and risk of suicide attempt [10, 18, 23]. However, each study classified suicide attempts by investigating different timeframes and reported distinct summary statistics. For example, Keyes et al. (2013) looked at suicide attempts that occurred within the past 12 months. They reported an odds ratio of 0.38 (95%CI; 0.15-0.97), suggesting hormonal contraceptive users showed a 62% reduction in odds of experiencing a past-year suicide attempt when compared to women using non-hormonal contraceptive methods [23]. Skovlund et al (2018)

quantified risk of first suicide attempts. They reported a hazard ratio of 1.97 (95%CI; 1.85-2.01), meaning the risk of first suicide attempt in women taking hormonal contraceptives was nearly double that in women who had never used hormonal contraception [10]. Vessey et al. (1985) looked at suicide attempts in participants without restriction on when the attempt occurred or whether it was the first attempt or not. A chi-squared test indicated insufficient evidence for an association between hormonal contraceptive use and risk of suicide attempt (chi square 3.1, d.o.f.=1) [18].

The association between hormonal contraceptive use and attempted suicides differed according to type of hormonal contraceptive being used. For example, Skovlund et al (2018) reported a positive association between use of combined OCP and first suicide attempt when compared with never use (relative risk of 1.91 with 95%CI; 1.79-2.03) [10]. Relative risk estimates for oral combined products with 20-40 micrograms of estrogen did not differ significantly from estimates for oral combined products with 30-40 micrograms of estrogen and Levonorgestrel. A positive association was found between risk of first suicide attempt and use of all types of progestin-only pills when compared with never use (relative risk of 2.29 with 95%CI; 1.77-2.95), but the risk did not differ significantly from risk estimates for combined OCPs.. For non-oral combined products authors reported the patch showed a relative risk of 3.28 (95%CI; 2.08- 5.16) and the vaginal ring showed a relative risk of 2.58 (95%CI; 2.06-3.22) [10]. Keyes et al (2013) calculated odds of past-year suicide attempt with progestin-only hormonal contraceptives (i.e. Depo-Provera or Norplant). The odds ratio of 1.6 (95%CI; 0.4- 6.1), while not statistically significant, was quite different from their earlier odds ratio of 0.38 (95%CI; 0.15-0.97), which accounted for OCP, patch, ring, Depo-Provera and Norplant together [23].

There was some association according to duration of hormonal contraceptive use and attempted suicide. Skovlund et al. (2018) observed a trend in their data for how risk of suicide attempt changed with duration of hormonal contraceptive use, whereas Vessey et al. (1985) did not [10,18]. Keyes et al. (2013) did not provide sufficient data to explore this relationship. Results from Skovlund et al (2018) show the relative risk of first suicide attempt increased sharply following initiation of hormonal contraceptive use when compared with never use. The relative risk was at least double that in never users throughout the first year of hormonal contraceptive use, after which the risk decreased gradually but remained approximately 30% higher than that in never users for up to 7+ years of use [10]. The exact risk ratios and their corresponding confidence intervals were not provided in the paper.

Age of participants did seem to influence the association between hormonal contraceptive use and attempted suicides in some cases. Both Skovlund et al. (2018) [10] and Keyes et al. (2013) [23] found that risk of suicide attempt was higher amongst younger participants; Vessey et al. (1985) did not stratify their results according to participant age. According to Skovlund et al (2018), participants aged 15-19 years and using hormonal contraceptives showed the highest relative risk of first suicide attempt compared with never users, with a hazard ratio of 2.06 (95%CI; 1.92-2.21) [10]. Risk estimates among women aged 20-24 and 25-33 were similar: 1.61 (95%CI; 1.39-1.85) and 1.64 (95%CI; 1.14-2.36) respectively [10]. Keyes et al (2013) reported on different waves of the National Longitudinal Study of Adolescent Health. Their data showed hormonal contraceptive use was not protective against suicide attempts in participants aged 18-28 years but was protective against suicide attempts in participants aged 25-34 years (OR 0.31, 95% CI: 0.15, 0.66) [23].

Association between hormonal contraceptive use and completed suicides

Seven studies of five different populations presented data on the association between hormonal contraceptive use and completed suicides [10,11, 19-22, 24]. Two studies reported different follow-up periods for the Nurses' Health Study [21,22] and two reported on different follow-up periods for the Royal College of General Practitioners' Oral Contraception Study [11,20]; to avoid double counting participants in these narrative comments, we used results from the longer follow-up time for both these studies, however, findings from all studies are presented individually in Table 1. Skovlund et al. (2018) calculated a hazard ratio of 3.08 (95%CI; 1.34-9.08), suggesting deaths by suicide occurred at three times the rate among women taking hormonal contraceptives compared with never users [10]. In the 36 years follow-up of the Nurses' Health study, Charlton et al (2014) calculated a hazard ratio of 1.41 (95%CI; 1.41—1.87) [22]. This indicated a 40% higher rate of completed suicide amongst users of oral contraception compared to never users of hormonal contraception.

Vessey et al. (1989) reported the relative risk of suicide in women using oral contraception compared to women using a non-hormonal intrauterine device as 1.1 (95%CI 0.3-3.6) [19], while Hannaford et al. (2010) (high quality study) reported a relative risk of suicide in women using oral contraception compared to never users as 1.26 (95%CI; 0.73-2.18) [11]. Neither of these results reached statistical significance. The International Collaborative Post-Marketing Surveillance of Norplant (2001) identified fewer suicides in Norplant users (n=2) compared to women using non-hormonal intrauterine devices or sterilization as contraception (n=6), with a mortality rate ratio of

0.33 (95%CI; 0.34-3.70) [24]. None of the studies reported data on changes in the association between hormonal contraceptive use and risk of completed suicides based on participants age. The association between type of hormonal contraceptive used and completed suicides was inconclusive. Of the papers that reported on completed suicides as an outcome, only Skovlund et al. (2018) stratified their results according to type of hormonal contraceptive used. They report the patch, vaginal ring and progestin-only contraceptives conferred a greater risk of suicide than combined OCPs, however the specific data was not provided [10].

The association between duration of hormonal contraceptive use and completed suicides was also inconclusive. Three studies reported on how the association between hormonal contraceptive use and risk of suicide changed based on duration of use; none of these studies observed a clear trend in their data [11,22, 24]. The remaining two studies did not stratify their findings according to duration of use [10, 19]

Quality Appraisal

All included articles were longitudinal cohorts therefore the JBI Critical Appraisal Checklist for Cohort Studies was used to classify studies as having an overall low (++), moderate (+) or high (-) risk of bias. Five (55.6%) studies were rated as low risk of bias [10,11, 20-22] ; three (33.3%) were rated as moderate risk [18,19,23] and one (11.1%) was rated as high risk [24]. Studies of low quality (moderate or high risk of bias) were either not adequately powered to detect an effect (n=2) [19, 24], identified few confounding variables (n=1) [18], did not provide information on how they accounted for participants lost to follow up (n=1) [23] or had high heterogeneity both within and across comparison groups (n=1) [24]. High quality studies [10,11, 20-22] used reliable and valid methods to measure the outcome of interest, considered a range of confounding variables, and were sufficiently powered for statistical analyses. A table presenting the quality assessment of individual studies is included in Appendix 5.

Discussion

Our review found there was substantial variability in the relationships reported between hormonal contraceptive use and suicide risk. Out of the three studies that reported on risk of suicide attempt, one found no association between hormonal contraceptive use and suicide attempt [18], the second found hormonal contraceptive use to have a protective effect on past-year suicide attempts [23] and the third study concluded hormonal contraceptives increased risk of first suicide attempt [10]. Of the five studies that reported on completed suicides, two [10,22] found an increased risk of suicide amongst hormonal contraceptive users. Three studies reported effect sizes with confidence intervals that crossed one and suggested no association [20], a trend towards increased risk [11] and a trend towards a protective effect [24] respectively. The overall quality of evidence was moderate to high.

Inconsistencies in the results could be due to several reasons. Firstly, studies varied in participant selection. Only two of the nine studies [10,23] used population-based samples but one of these was of low methodological quality as the authors did not discuss how incomplete follow-up was addressed [23]. Four populations were comprised of women recruited from family planning clinics or general practitioner clinics [11, 19, 22, 24] which may reduce the generalizability of the risk estimates reported. Secondly, many studies reported small numbers of attempted and completed suicides, as these outcomes are relatively rare and are also often poorly defined, misclassified, and under-reported [25]. Importantly, only one study considered participants' concurrent depressive symptoms [23]. While the most common theory in the literature is that the relationship between hormonal contraception and suicide risk is mediated by depression, this relationship is likely to be multifactorial. There are environmental and social factors that must be considered as confounders [26] and none of the studies adjusted for other important factors in suicide such family history of mental health disorders or childhood adversity [26].

There is some evidence suggesting a higher risk of attempted suicides at initiation of hormonal contraceptive use compared to continued use [10, 23]. As such, adolescent women experienced the highest risk. Skovlund et al. (2018) suggested this may be due to adolescent women being especially sensitive to the effects of hormonal contraception or to selective attrition where women who experienced side effects, including those related to mental health, had stopped use or been lost at follow up [10]. It should also be noted that the choice of contraceptive method is not random and women who choose different forms of hormonal contraceptive methods may differ systematically [27]. Thus, results of studies that only examined oral contraception as the

exposure, or only considered non-hormonal barrier methods as the control may not be generalizable to all women using hormonal contraception or all women using non-hormonal contraception. There is evidence that women with common mental disorders may choose less effective contraceptive methods and use contraception less effectively [28,29]. However, none of the studies included in this review assessed mental state at contraceptive initiation, reason behind particular contraceptive choice or adherence to the prescribed contraceptive.

To the best of our knowledge, this is the first systematic review to assess evidence for an association between hormonal contraceptive use and attempted or completed suicides. This review was conducted according to PRISMA guidelines, and used pre-specified study inclusion and exclusion criteria to reduce the possibility of selection bias from screeners' existing knowledge on the topic. All studies found were assessed for quality using a validated tool and were synthesized in our results. However, this review has a number of limitations. The findings of individual studies showed high variability in sample size, type of hormonal contraceptive used and outcome measurement. Therefore, a meta-analysis was not appropriate and studies were synthesized narratively only [17]. Four out of the nine included studies were classified as low quality. As they were not excluded from the review, their findings may have affected the conclusions drawn. Only one included study was conducted in a low and middle income country context and all articles were in English language; thus, it was not appropriate to make assertions about the association between hormonal contraceptive use and suicide for settings across the world. Finally, only one study [10] was designed with the primary objective of exploring the association between hormonal contraceptive use and suicide attempts or suicide. Most of the other studies were designed to look at the relationship between hormonal contraception and overall mortality [11, 19, 22, 24]. Thus, it is possible that these studies were not adequately designed or powered to find an effect.

Conclusions

This systematic review was unable to draw a firm conclusion regarding an association between hormonal contraceptive use and attempted or completed suicides, due to the small number of studies found and the lack of consideration of key confounding variables. Going forward, researchers investigating this topic are encouraged to use population-based samples to take efforts to control for important confounders and consider low income as well as high income settings. This is particularly necessary given the large number of women taking hormonal contraceptives throughout the world. Several of the reported cohorts began decades ago and while this allowed for data to be collected long-term (which is especially important given suicide

is a rare outcome), it also restricted the exposure to older forms of hormonal contraception in many cases. New studies are needed to investigate the effects of more recent hormonal contraceptive methods on suicide risk.

Declarations

Funding

No funding was required for this study

Conflict of interests

The authors declare that they have no completing interests

Ethics approval

Ethics approval for this study was obtained by the London School of Hygiene and Tropical Medicine. This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Data and material for from this study can be obtained from the corresponding author.

Code availability

Not applicable

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