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Research paper

Association of oral contraceptive use with suicidal behavior among representative Korean population: Results from Korea National Health and Nutrition Examination Survey (2007–2016)

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ABSTRACT

Introduction: The association of suicide with the use of oral contraceptives (OC) is unknown in the Asian population. We aimed to evaluate the association of OC use and suicidal behavior in a nationally representative population of Korean women.

Method: Of the 44,501 women who participated in the Korea National Health and Nutrition Examination Survey (KNHANES) (2007–2016), 27,067 women aged 20 years or older who had completed information on OC use and suicidal behavior were included. Women with a history of cancer were excluded. Compared to non-users of OC, odds ratios (ORs) for suicide attempt/ideation were calculated using a multivariable logistic regression among OC users, with testing of the interaction term of OC use and history of depression. We also conducted a stratified analysis by history of depression.

Results: A total of 4,067 women (14.0%) reported they had suicide ideations or had attempted suicide, respectively. OC use was associated with an increased prevalence of suicidality (OR = 1.13, 95% CI 1.00–1.24) after adjustments for age, demographic factors, age of menarche, and lifestyle behaviors. When stratified by history of depression diagnosis, ORs linearly increased as the total duration of OC use lengthened among women with a history of depression; however, women without a history of depression showed peaked OR at 4- to 12-month use.

Conclusion: There is an increased association between OC use and suicidality and the pattern of the relationship differs depending on whether there is a history of depression.

1. Introduction

Suicide is a major public health problem that has been and remains large concern. Globally, suicide is the leading cause of overall death and the second-leading cause of death for those aged 15–29 (World-Health-Organization, 2011) and based on current trends, it is estimated that 1.53 million people will die from suicide in 2020 (Bertolote et al., 2003). In terms of productivity loss, the Global Burden of Disease Mortality and Causes of Death Collaborators have reported that suicide caused approximately 34 million years of life lost (YLL) (GBD-Risk-Factors-Collaborators et al., 2015). Among developed countries, Korea showed the highest suicide rate among developed countries and nearly 26 deaths per 100,000 of the population in 2016;(Shin et al., 2016), a two fold higher than that of the US (Center-for-Disease-Control-and-Prevention, 2015).

Suicide statistics also vary in its ideation and attempt rates; in a cross-national comparison, the lifetime prevalence of suicide ideation varied between 2.1% and 18.5%, and suicide attempt ranged as low as 0.7% to as high as 5.9% by country and other risk factors, such as sex (Bertolote et al., 2003). It is well established that suicide ideations and attempts are approximately two times more frequent in women than men (Kessler et al., 1999). To evaluate this gender difference, several studies have focused on various female hormonal factors such as menstrual cycle (Baca-Garcia et al., 2003), serum level of estradiol and progesterone (Baca-Garcia et al., 2010), and estrogen receptor genes (Giegling et al., 2008; Ostlund et al., 2003); most of them found that low activity of estrogen may be linked to low serotonergic activity in the brain, and a possible consequence from oral contraceptive (OC) use that can affect suicidal ideation and attempts (Bertolote et al., 2003). Six previous studies (Beral et al., 1999; Charlton et al., 2014; Colditz, 1994; Hannaford et al., 2010; Skovlund et al., 2018; Vessey et al., 1989) have evaluated the relation between OC use and overall mortality

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including death caused by suicide solely in Caucasian populations (Supplementary Table 1). Of those, four earlier works (Beral et al., 1999; Colditz, 1994; Hannaford et al., 2010; Vessey et al., 1989) addressed no statistically significant associations. However, the later two studies with both relatively higher prevalence of suicidality in population found significantly increased hazard ratio (HR) for suicide among OC users compared to non-users: Charlton et al. (2014) reported the increased risk (HR = 1.41, 95% CI 1.05–1.87) of suicide among US OC-users compared to non-users, and a recent study in Denmark also found a positive association between OC use and suicide (HR = 3.08, 95% CI 1.34–7.08).

In addition, depression, the most common condition associated with suicide, affects lifetime risk of suicide, ranging 2–15% (Friedman and Leon, 2007). Given that approximately 25 times greater risk for suicide exists among people suffering from depression compared to general population, the association between OC use and suicidality might be affected by the presence of comorbid depression (Breitbart, 1990). However, none of the previous works compared the differential effect of depression. Hitherto, more comprehensive assessment on the association between oral contraceptive and suicidality considering comorbid depression is needed in diverse population with higher suicidal rate. Therefore, our objective of this study was to evaluate the association of OC use and suicidal behavior among a nationally representative sample of Korean women, considering the mediating effect of depression.

2. Materials and methods

2.1. Study participants

We used data derived from the Korea National Health and Nutritional Examination Survey (KNHANES) between 2007 and 2016. Since 1998, KNHANES has been an ongoing study that aims to capture the health status of Korean population and to assess the trends and prevalence of various chronic diseases. As a nationwide cross-sectional survey, its target population includes nationally representative non-institutionalized participants, using a multi-stage clustered probability method; approximately 200,000 primary sampling units (PSUs) were defined by geographical locations in the Republic of Korea, and the final 192 PSUs were selected from them. Precise information about the design of KNHANES can be found elsewhere (Kweon et al., 2014). Considering the complex survey design, post-hoc stratification, and non-response to survey, we created sample weights to compute all statistics of this study. Initially, we used the data of 44,501 women who joined the survey from 2007 to 2016. Of those, we excluded women who were aged under 20 years (N = 9460), did not provide valid information on OC use (N = 3366) or accurate information on suicide (N = 3439), or with cancer history (N = 1169). The final analyses included a total of 27,067 women (Fig. 1).

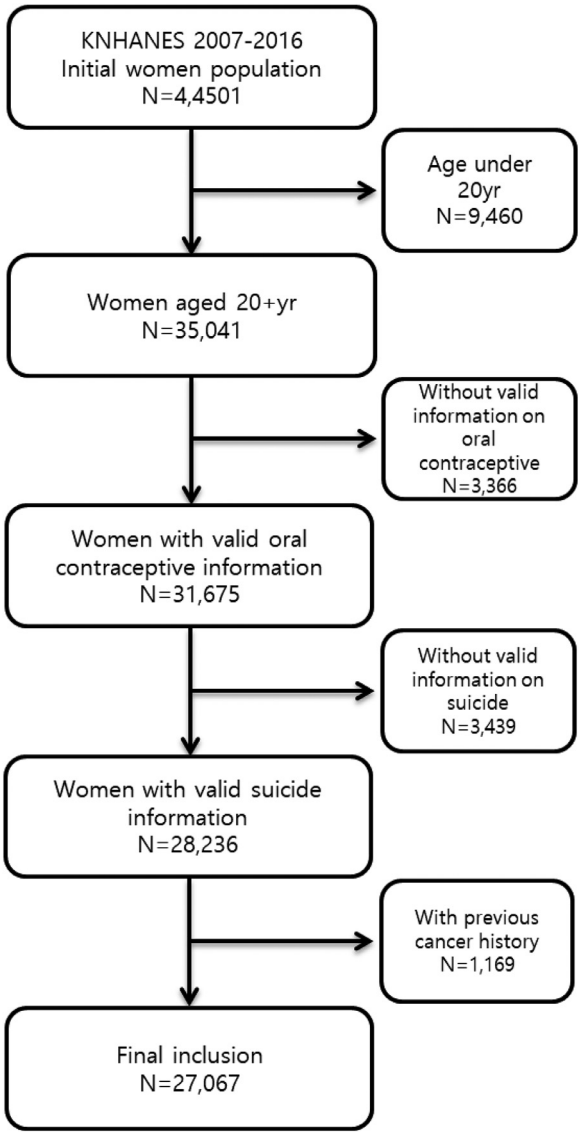

Fig. 1. Selection of participants for the association between oral contraceptive and suicide behavior in KNHANES (2007–2016).

2.2. Measurements

KNHANES was formulated through trained interviewers and structured questionnaires to conduct individual interviews and adhered to standardized protocols. The survey was comprised of health interview, nutrition survey, and health examination. Participants were asked about demographic and social factors; medical conditions, including depression diagnosis and treatment; daily stress; suicidal ideation/attempt; medical utilization, including health screening and vaccination; and lifestyle factors such as alcohol and cigarette use. Women were additionally asked about female reproductive factors such as menarche, menopause, pregnancy, breastfeeding, use of OC, and hormone replacement therapy. The question regarding OC use was phrased as, "Have you ever used an oral contraceptive for at least one month?" During the entire survey, women were asked if they had ever consumed OC. However, total duration of OC use was queried only between 2007 and 2012. Specifically, during 2007–2009, women were asked to report multiple time points regarding initiating and suspending the use of OC to calculate the total duration of OC consumption; and between 2010 and 2012, women were asked to report the total duration of OC use instead of specific time points. With this information, we classified the duration of OC use, following the overall distribution of population, into quartile: less than 3 months, 4–12 months, 13–24 months, and 24 months or more. Suicidal ideation was asked as, "Within recent one year, have you ever seriously thought about killing yourself ?" and suicidal attempts were asked as, "Within recent one year, have you ever actually tried to kill yourself?" Both two items were queried without any change between 2007 and 2016. Anyone who answered "yes" to either suicidal attempt or suicidal ideation item, she was considered to have "suicidality". Depression history was measured by the following question; "Have you ever been diagnosed for depression by physicians?" Additionally, the age of first depression diagnoses and depression treatment were queried.

For covariates, age was obtained from personal identification numbers under participant consent. Education level was queried through interview. Household income, family number, cigarette smoking, alcohol use, and age at menarche were assessed via self-administered questionnaire.