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The impacts of reproductive experiences on the risks of cognitive decline and dementia in elderly women

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Abstract

The impacts of reproductive experiences on the risks of cognitive decline and dementia in elderly women

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Background: There is substantial evidence on the impacts of sex hormones on the brain and cognitive functioning. Although the number of pregnancies have been associated with the risk of cognitive decline and/or dementia in elderly women, such

associations have not been consistently replicated, and the impacts of pregnancy loss have been barely investigated. The changes in sex hormones induced by pregnancy loss are distinct to those associated with pregnancy followed by childbirth.

Objective: To investigate the different impacts of pregnancy from childbirth and pregnancy loss on the risks of cognitive decline and dementia in elderly women.

Methods: We conducted this retrospective cohort study (N = 2,540) as a part of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD). Reproductive history was obtained from the participants, and women who had hormone replacement therapy, hysterectomy or oophorectomy were excluded. We measured global cognition using the Mini Mental State Examination (MMSE) and the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological assessment battery total score I (CERAD-TS I). We diagnosed dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and mild cognitive impairment (MCI) according to the consensus criteria from the International Working Group on MCI.

Results: Higher number of childbirths and lower numbers of pregnancy loss were associated with a lower MMSE score and CERAD-TS ($p < 0.001$). 5 or more experiences of childbirth increased the risk of dementia ($p < 0.01$) and the experience of loss of pregnancy was protective against dementia ($p < 0.001$).

When we analyzed the risk of dementia separately by causes, pregnancy loss lowered the risk of Alzheimer's dementia, vascular dementia, and other dementia.

Conclusions: Experiences of childbirth and pregnancy loss were closely associated with cognitive functioning and dementia risk. Hormone replacement therapy may reduce the risk of dementia if we modify it, based on the hormonal changes in pregnancy loss.

Keyword: Reproductive experiences, Childbirth, Loss of pregnancy, Dementia, Cognition, Risk factors

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1. Introduction

Cognitive disorders such as dementia are more prevalent in women than in men (Kim, et al., 2011, Matthews, et al., 2013). After adjusting age and education, female gender was still found to be an independent risk factor of dementia in many prospective studies (Launer, et al., 1999, Plassman, et al., 2011). The role of global Alzheimer's disease (AD) pathology to the clinical diagnosis of AD differed for men and women; each additional unit of AD pathology was associated with a nearly 3-fold increase in the odds of clinical AD in men, whereas a more than 20-fold increase in the odds of clinical AD was observed in women (Barnes, et al., 2005). Animal models of AD also exhibited differences between sexes in neuropathology; females showed earlier and more robust neuropathological changes compared to males (Vest and Pike, 2013). Therefore, women may be more vulnerable to cognitive decline and/or dementia than men, and the factors underling this vulnerability for women may improve our understanding of the pathogenesis of dementing illnesses like AD.

The most obvious difference between men and women may be their reproductive systems. Women have various reproductive experiences, such as menstruation, pregnancy and childbirth. These reproductive experiences are frequently

associated with changes in brain and cognitive functions. For example, overall brain volume of pregnant women decreases by as much as 8% across gestation and is subsequently normalized by six months after delivery (Oatridge, et al., 2002). Pregnant women frequently reported forgetfulness (about 80%) and reading difficulties (more than 50%) (Poser, et al., 1986), which also continued for three months, or even longer, after delivery (Brett and Baxendale, 2001). Reproductive experiences affect not only the cognition of fertile-aged women, but also the risk of cognitive decline and dementia in elderly women. As of August 2016, there were ten studies investigating the association of reproductive experiences with cognitive impairment and/or dementia in elderly women (four case-control studies, three retrospective cohort studies and three prospective cohort studies). Colucci et al. (Colucci, et al., 2006) reported that the number of pregnancies was positively correlated with the risk of AD and negatively correlated with the age-at-onset of AD in women. Beeri et al. (Beeri, et al., 2009) found that the number of children born was associated positively with the density of neurotic plaque and neurofibrillary tangle of postmortem brain in women. Ptok et al. (Ptok, et al., 2002) reported that women who have had one or more childbirths have a higher risk of AD. This was not found for men.

However, there were several methodological limitations in the previous studies. Firstly, they did not examine several key

reproductive experiences. Women's reproductive experiences include adverse pregnancy outcomes, such as loss of pregnancy and stillbirth. However, only two studies investigated the association of the number of pregnancy losses with cognitive function in the elderly (Colucci, et al., 2006, Li, et al., 2015), and there was no study on stillbirths. Secondly, nine out the ten studies were conducted in developed countries, where women have fewer pregnancies compared to underdeveloped or developing countries (Bloom and Freeman, 1986). The mean number of live birth in these regions ranged from 1.0 to 2.5 (Beeri, et al., 2009, Bove, et al., 2014, Fox, et al., 2013, Geerlings, et al., 2001, Ptok, et al., 2002) and the mean number of pregnancy losses (described only one study) was 0.3 (Colucci, et al., 2006). Therefore, effects of multiple reproductive experiences on the risk of cognitive impairment or dementia may have not been fully investigated. Thirdly, there were no studies on the association of reproductive experiences with various types of dementia other than AD. Fourthly, previous studies measured global cognitive functions using only MMSE, which is very brief and insensitive to the frontal function. Lastly, the sample sizes were relatively small in most of the studies. The number of participants was below 100 in three studies and below 600 in four studies. Only three studies had a sample size larger than 1,000 subjects.

To overcome these limitations, we conducted a large-scale population-based prospective cohort study on 2,540 elderly Korean women living in South Korea. The study obtained comprehensive information about reproductive experiences, results of neurocognitive tests and clinical diagnosis (mild cognitive impairment, dementia and dementia subtypes) of participants. This was used to investigate the impacts of reproductive experiences on the risks of cognitive decline and dementia in elderly women.

2. Methods

2.1 Study population

Participants were recruited from the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) (Park, et al., 2007). A total of 10% of the residents aged 60 years or older (N = 13,749) were randomly sampled as the participants from the residential rosters of 14 districts across South Korea, in order to capture national variations. Among the 6,831 participants who completed the baseline assessment of the KLOSCAD conducted from February 2010 to April 2011, 3,917 (57.3%) were women. Among them, 3,411 (87.1%) provided full reproductive history and completed diagnostic assessments for cognitive disorders, including comprehensive neuropsychological tests. From these, 871 women who either took hormone replacement therapies (N = 525), oophorectomy (N = 230) or hysterectomy (N = 465) were excluded. Subsequently, 2,540 women were included in this analysis. The written informed consent was obtained from all the participants recruited in the study or the caregivers of the participants diagnosed with dementia. The KLOSCAD was approved by the Institutional Ethics Review Board of the Seoul National University Bundang Hospital.

2.2 Assessments

Geriatric psychiatrists with expertise in dementia research administered a standardized diagnostic interview, including detail medical histories, physical and neurological examinations, and laboratory tests. These tests included complete blood cell count, chemistry profile, serological test for syphilis, echocardiogram, chest x-ray and apolipoprotein E genotype to each subject, according to the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) Clinical Assessment Battery (CERAD-K-C)(LEE, et al., 2004) and the Mini International Neuropsychiatric Interview (MINI) (Yoo, et al., 2006). A research neuropsychologist or trained research nurse conducted neuropsychological assessments, including the CERAD Neuropsychological Assessment Battery (CERAD-K-N) and Frontal Assessment Battery (FAB) (Chandler, et al., 2005,Dubois, et al., 2000). For the measurement of global cognitive state, six test scores in CERAD-K-N were summed to calculate the CERAD total score I (CERAD-TS I) according to the method proposed by Chandler et al. (Chandler, et al., 2005). The CERAD-TS I is reported to show a good reliability and validity for AD and amnestic mild cognitive impairment (aMCI) patients and showed a superior discriminability to MMSE on normal aging, MCI, and the early stage of dementia (Chandler, et al., 2005,Ehrensperger, et al., 2010). The Short Geriatric Depression

Scale (S-GDS) (Yesavage, et al., 1983) was self-administered to evaluate the severity of depressive symptomes. Brain computed tomography or magnetic resonance imaging (T1-weighted, T2-wighted, FLAIR) were conducted for the subjects who were diagnosed to have dementia to determine the subtypes of dementia.

A comprehensive history of reproductive experiences was obtained by research clinicians using a study-specific questionnaire that included the number of pregnancies, the number of childbirths, the number of stillbirths, the number of pregnancy losses (including both natural and induced abortion), the ages of the first and the last births, the ages of menarche and menopause, and whether they breast fed the child (or children). Menopause was defined by amenorrhea for more than 12 months, according to the standard criteria of the World Health Organization (Organization, 1981).

2.3 Diagnosis

The diagnosis of dementia was based on the DSM-IV-TR criteria. AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann, et al., 1984). Vascular dementia (VD) was diagnosed according to the National Institute

of Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignementen Neurosciences (NINDS-AIREN) (Román, et al., 1993). In this study, dementia subtypes other than AD or VD were grouped into other types of dementia. MCI was diagnosed according to the consensus criteria from the International Working Group on MCI (Albert, et al., 2011, Petersen, 2004).

2.4 Statistical Analysis

Descriptive statistics were used to observe the demographic, clinical, and reproductive characteristics of the participants. The association of female reproductive experiences and cognitive function was examined via a stepwise multiple linear regression analysis to investigate which of the reproductive factors have a meaningful association with late life cognitive functions. The neuropsychological test scores were used as the dependent variables and the female reproductive experiences was entered as the independent variables. Other variables with a possible effect on cognitive functions, such as age, total years of education, history of diabetes mellitus, and S-GDS score, were also entered as independent variables along with the female reproductive experiences. Lastly, logistic regression analyses were used to examine the association between reproductive factors that have a significant effect on cognitive functions and clinical diagnosis

such as MCI, dementia and its subtypes. In multinominal logistic analysis, reproductive factors were entered as categorical variables to define the number of each reproductive experience that will increase the risk of dementia. Age, total years of education, history of diabetes mellitus, and S-GDS score were adjusted. All data was analyzed with the Statistical Package for Social Sciences, v18 (SPSS Inc., Chicago, IL).

3. Results

3.1 Characteristics of the participants

Table 1 shows the demographic characteristics and the retrospective data on reproductive experiences of participants from KLOSCAD. The mean age of the participants was 71.37 (standard deviation (SD) = 7.11). The mean total years of education was 5.67 (SD = 4.74). The average S-GDS score was 5.54 (SD = 3.71). A total of 19% of elderly women (N = 479) were classified as having a history of diabetes mellitus. The average number of births was 3.74 (SD = 1.72, range = 12), and the average number of pregnancy losses (including both natural and induced pregnancy loss) was 1.61 (SD = 1.89). The mean age at menarche was 16.80 years (SD = 2.24), and that of menopause was 50.09 years (SD = 5.09). The mean age at first birth was 24.33 years (SD = 3.57, range = 26), and that of last birth was 32.54 years (SD = 4.89, range = 33).

3.2 Reproductive experiences and late life cognitive decline

In the partial correlation analysis that controlled age, years of education, history of diabetes mellitus, and S-GDS, the MMSE score was positively correlated with the number of pregnancy

losses (r = 0.079, p < 0.001) and the age at first birth (r = 0.048, p = 0.017), and negatively correlated with the number of childbirths (r = -0.110, p < 0.001) and age at last birth (r = -0.068, p < 0.001). The CERAD-NP TS-I score was also positively correlated with the number of pregnancy losses (r = 0.119, p < 0.001) and the age at first birth (r = 0.043, p = 0.032), and negatively correlated with the number of childbirths (r = -0.077, p < 0.001) and the age at last birth (r = -0.42, p = 0.037). The age at menarche and menopause were not correlated with any of the cognitive test scores.

The stepwise multiple linear regression analysis was used to assess the relative contribution of the reproductive factors on cognitive test scores. MMSE and CERAD-TS I were used as the dependent variables. Reproductive experiences (the age at menarche, the age at menopause, the number of childbirths, the number of pregnancy losses, the age at first birth, and the age at last birth) and possible confounders for cognitive tests (age, education, history of diabetes mellitus, and S-GDS) were entered as independent variables. For the MMSE score, age, years of education, S-GDS, the number of pregnancy losses, and the number of births were selected as significant predictors. The number of pregnancy losses (B = 0.13, 95% confidence interval (CI = 0.070.20, p < 0.001) increased whereas the number of births (B = -0.25, 95% CI = -0.34-0.16, p < 0.001) decreased the MMSE score (Table 2). For CERAD-TS I, age, years of

education, history of diabetes mellitus, S-GDS, the number of pregnancy losses, and the number of births were selected as predictors. The number of pregnancy losses (B = 0.63, 95% CI = 0.420.83, $p < 0.001$) increased whereas the number of births (B = -0.53, 95% CI = -0.81-0.26) decreased the CERAD-TS I score (Table 2).

Figure 1 shows the dose-response relationships between reproductive factors and the mean cognitive scores. The z-scores of MMSE and CERAD TS-I are shown on the y-axis. The number of childbirths, scaled down to four groups (0-2 (N = 572), 3-4 (N = 1,234), 5-6 (N = 531), and 7 and more (N = 166)), are displayed on the x-axis. The number of pregnancy losses scaled down to three groups (0 (N = 799), 1 (N = 655), and 2 and more (N = 1,049)), are shown in three separate lines.

3.3 Reproductive experiences and the risk of dementia

We further investigated the impact of childbirth and pregnancy loss experiences on the risk of MCI and dementia. The number of childbirths was categorized into two groups; 0-4 and 5 or more childbirths. The number of pregnancy losses was categorized into two groups; none or 1 or more pregnancy loss(es). In KLOSCAD cohort, 772 and 124 participants were diagnosed as having MCI and dementia respectively. In

multinominal logistic regression analysis, adjusting age, education, cohort effect, history of diabetes mellitus and S-GDS, the risk of MCI was not associated with a high number of childbirths (OR = 1.05, 95% CI = 0.841.31) and the experience of pregnancy loss (OR = 0.96, 95% CI = 0.791.16). A risk of dementia was associated with a high number of childbirths (OR = 1.66, 95% CI = 1.072.56) and the experience of pregnancy loss (OR = 0.45, 95% CI = 0.300.68) (Table 3).

In 196 dementia patients, the number of patients with AD and VD were 96 and 11, respectively. We further analyzed the association between reproductive experiences and the subtype of dementia. The experience of pregnancy loss was significantly associated to the risk of AD (OR = 0.60, 95% CI = 0.380.95) and VD (OR = 0.08, 95% CI = 0.02) (Table 4). However, the relationship between high numbers of childbirths with AD and VD were not statistically significant. There were 17 dementia patients classified as having other dementia types (OD), which include FTD, DLBD, PDD and dementia NOS. The experience of pregnancy loss (OR = 0.36, 95% CI = 0.13) was associated with the risk of OD.

4. Discussion

The results of this study indicate a significant relationship between reproductive experiences and cognitive impairment in elderly females. The global cognitive function in elderly women was negatively correlated with the number of childbirths and positively correlated with the number of pregnancy losses. Furthermore, the risk of dementia was associated with the experiences of childbirth and pregnancy loss. Women who had five or more childbirths had a higher risk of dementia than women who had less than five births, and women with a loss of pregnancy had a lower risk of dementia than women without a loss of pregnancy.

Sometimes childbirth has a negative impact on the human brain. For example, 40-80% of women had mild and transient mood disturbance, 5-10% of women were diagnosed with postpartum depression and 0.1-0.5% of women had postpartum psychosis (O'Hara and McCabe, 2013). The above problems occur shortly after childbirth. On the other hand, the experience of childbirth for females was found to have a harmful effect on cognitive functions of old age decades later in this study. The impacts of childbirth experiences on the cognition in the elderly can be explained by the following biological mechanisms. Firstly, changes in hormones during childbirth might have detrimental

effects on the brain and decrease cognitive reserve. In pre-menopausal women who are not pregnant, the plasma concentration of estradiol is lower than 0.25ng/ml. The level of plasma estrogen increases gradually up until the end of pregnancy, and is more than 100 times higher than the level before pregnancy (Cunningham, 2014). Although estrogen was known to have a positive effect on cognition functions (Tang, 2004), an extremely increased level of plasma estrogen in late pregnancy may not be beneficial, or may be even harmful to cognitive functions. The dose-response pattern of beneficial effects of estrogen on cognitive functions was observed to follow an inverted U shape in an animal study (Inagaki, et al., 2010). The administration of high doses of estrogen was ineffective for enhancing cognitive functions (Inagaki, et al., 2010). High levels of estrogen impaired cognitive functions associated with hippocampus, amygdala and prefrontal cortex (Barha and Galea, 2010), potentiated long-term depression of CA1 region and suppressed the level of cell proliferation in the dentate gyrus (Desmond and Levy, 2000, Ormerod and Galea, 2001). High-dose regimens of estrogen increased the inflammation of the brain and exacerbate neural injury (Nordell, et al., 2003, Strom, et al., 2011). Furthermore, rapid hormonal changes after childbirth may have a deleterious effect on the brain. Concentrations of estrogen and progesterone, which are extremely elevated during pregnancy, fall abruptly after delivery. If estrogen has neuroprotective effects,

neurons may be vulnerable to neurotoxic injury by the abrupt withdrawal of estrogen. Like estrogen, progesterone also has diverse roles on the brain via direct and indirect effects. Progesterone has a high affinity for GABA receptors and inhibitive effects on neuron. Therefore, the rapid decrease of progesterone also increases the excitability of the brain. This was proposed as one of the explanations for increased risk of seizures in postpartum women (Brett and Baxendale, 2001). Cortisol is another hormone that experiences an alteration of concentration during pregnancy and it is closely associated brain damage and cognitive dysfunction (Lupien, et al., 1998). The hippocampal neurons with high cortisol levels are more sensitive to damages such as hypoxia, hypoglycemia and high glucocorticoid levels lead to an atrophy of hippocampal neurons (Landfield, et al., 1981). Like sex hormones, concentrations of cortisol gradually increased during pregnancy; 149ng/ml (mean) at 12 weeks, 352ng/ml at 26 weeks and 706ng/ml during labor (Carr, et al., 1981). However, cortisol levels fall less dramatically compared to the sex hormones and can remain raised for several weeks after delivery (Brett and Baxendale, 2001, Willox, et al., 1985). Progesterone is a strong antagonist of the mineralocorticoid receptor and a weak antagonist of glucocorticoid (Rupprecht, et al., 1993), on which cortisol acts. Therefore, relatively sustained high levels of cortisol may cause long-lasting damage to the brain, acting jointly with the abrupt decrease of plasma progesterone. In summary,

extremely high levels of estrogen, an abrupt withdrawal of reproductive hormones or cortisol induced damage during childbirth, may have acute detrimental effects on the brain and contribute to decreased cognitive reserves.

Secondly, childbirth experiences may have deleterious effects on the cognition of women in late life by inducing lifelong changes in the baseline level and the sensitivity of sex hormones. Although plasma concentrations of both estradiol and progesterone decrease abruptly to the non-pregnant level within four days, the plasma estrogen concentration in women who have had an experience of childbirth was lower than that in women who have never given birth (Barrett, et al., 2014, Bernstein, et al., 1985). This suggests that childbirth experiences may influence the plasma level of estrogen over lifetime of women. Bridges and Byrnes supported this speculation by showing that primiparous rats have reduced circulating levels of estradiol and sensitivity to estrogen during the proestrous stage of the estrous cycle compared to nulliparous rats (Bridges and Byrnes, 2006). Also in postmenopausal women, inverse associations were observed between parity and the level of estrone sulfate, the most abundant plasma estrogen in postmenopausal women (Hankinson, et al., 1995). It has been well established that women who have been exposed low endogenous estrogen by surgical menopause showed a faster decline in global cognition and an increased risk of dementia (Bove, et al., 2014, Rocca, et al., 2007). Considering

the neuroprotective effects of estrogen in physiological concentrations (Inagaki, et al., 2010), a decrease in estrogen levels and/or sensitivity of the estrogen receptor in women with multiple childbirths contributes to decreasing positive effects of estrogen on lifetime cognition. As a result, childbirth experiences may decrease cognitive reserves and increase the risk of cognitive impairment in old age.

In contrast to the impact of childbirth to cognitive functions in the elderly, loss of pregnancy had a protective effect on cognitive impairment and the development of dementia in old age. There have been two studies that have investigated the relationship between pregnancy loss and cognitive impairment in the elderly. In a case-control study of Italian women, the number of pregnancy losses was not different between AD patients and controls (Colucci, et al., 2006). However, the number of participants (AD patients were 204 and controls were 201) was small and participants had few experiences of pregnancy loss (mean number of pregnancy loss was 0.3 ± 0.8). On the contrary, the women without pregnancy loss had a higher risk of cognitive impairment as defined by MMSE, compared to women who experienced pregnancy loss 1-2 times, in a population-based study of Chinese women aged 60 and older (Li, et al., 2015).

Furthermore, loss of pregnancy was not only associated with cognitive function in the elderly but also with the risk of dementia development in our study. Based on the results of

previous and current studies, we can assume that a loss of pregnancy has the effect of enhancing cognitive reserves and decreasing the risk of cognitive impairment in the elderly.

Pregnancy loss includes spontaneous abortion (also known as miscarriage) and induced abortion, and usually happens in the first trimester. More than 80% of spontaneous abortions and more than 90% of induced abortions occur within the first 12 weeks of gestation (Cunningham, 2014). Therefore, the women who have experienced pregnancy loss were not exposed to biological changes experienced by women giving birth. They did not experience extremely increased levels of plasma estrogen and an abrupt withdrawal of reproductive hormones. Instead, women who experience pregnancy loss were exposed to lower concentrations of estrogen for a shorter period of time compared to women who experience childbirth. Unlike extremely high levels, mildly increased levels of estrogen have a positive effect on the cognition. In an animal study, 15-20 μg/kg of estradiol of 17β-estradiol facilitated object placement tasks, while lower and higher doses were ineffective (Inagaki, et al., 2010). In premenopausal women, estradiol-based oral contraceptive users showed an enhanced memory during the active pill phase (Mordecai, et al., 2008). A history of hormonal contraceptive use was positively associated with global cognition and verbal memory in postmenopausal women. This association was

strongest for more than 10 years of use (Karim, et al., 2016). Considering the effects of estrogen on the cognition of women, the results of this study suggest that gradually increasing levels of estrogen during early pregnancy may enhance cognitive reserves and can be a way to prevent cognitive impairment in old age.

Interestingly, the impact of pregnancy loss on the risk of dementia was quite varied according to the types of dementia in this study. The risk of VD in women with the experiences of pregnancy loss was lower. However, the risk of AD was not affected by the experiences of pregnancy loss in women. Estrogen has neuroprotective effects against cerebral ischemia and infarction; attenuating superoxide release (Bruce-Keller, et al., 2000), increasing glutathione reductase (Urata, et al., 2006), reducing free radical production by increasing mitochondrial efficiency (Irwin, et al., 2008), increasing vasodilation and facilitating blood flow by increasing levels of eNOS protein and NO production, and inhibiting extracelluar Ca^{2+}influx to vascular smooth muscle in cerebral vessels (Salom, et al., 2001, Toung, et al., 1998). In a systematic review of animal studies, estrogens actually reduced lesion volume induced by experimental ischemia when administered to ovariectomized females and young adult males (Gibson, et al., 2006). Like estrogen, progesterone has neuroprotective effects against cerebral infarction. In a mouse model for cerebral ischemia induced by bilateral common carotid

artery occlusion, progesterone reduced TNF-α,improved levels of anti-oxidants such as lipid peroxidation, superoxide dismutase, catalase and glutathione peroxidase, and decreased cerebral infarct size compared to the control group (Aggarwal, et al., 2008). Epidemiologic studies also reported that the risk of stroke in women was lower than in men at least until the years of menopause, after which the levels of estrogen and progesterone decrease and the incidence of stroke increases (Murphy, et al., 2004). Therefore, we may cautiously assume that the beneficial effects of pregnancy loss on the risk of dementia may be, at least in part, related to the lifelong anti-ischemic action of estrogen and progesterone.

One of the major implications of this study is the observation that women with a high risk of dementia can be identified by their history of reproductive experiences. The cognitive functions and the risk of dementia in women who had 3-4 childbirths were not different when compared to those who had 0-2 childbirths. However, women who had five or more childbirths had lower cognitive functions and a higher risk of dementia compared to those who had less than five childbirths. There are many elderly women in Asia who have delivered children at least five times. A total of 28% of participants in this study experienced more than five births, and 23% of Chinese elderly women aged 60 years and older experienced full-term pregnancies five or more times (Li, et al., 2015). Therefore, it is

necessary to regularly assesse the cognitive functions of women with multiple childbirths and to detect cognitive impairment early. Furthermore, additional research is needed to develop interventions to prevent dementia for elderly women with multiple childbirths.

In addition, this study has raise a need for the modification of estrogen replacement therapy (ERT) designed for preventing dementia. The effects of ERT were different according to designs and the subjects of the therapy. Early observational and small experimental studies found ERT to be beneficial in reducing the risk of dementia (Daniel, 2013). In contrast, clinical trials conducted by the Women's Health Initiative (WHI) showed that ERT given to women aged 65 years and older had an adverse effect on the cognition and increased the risk of dementia (Espeland, et al., 2004, Shumaker, et al., 2003). Most clinical studies have been carried out with ERT only in postmenopausal women and failed to demonstrate the effectiveness of ERT in preventing dementia. However, the sensitivity and profile of the estrogen receptor in the brain were changed by the level of estrogen and reproductive experiences (Bridges and Byrnes, 2006), and the effects of estrogen on cognition may be different before and after menopause. Actually, Cache County Study showed that the women with estrogen therapy within five years of menopause had a 30% less risk of dementia, whereas the dementia risk was not reduced in women

who had initiated estrogen therapy five or more years after menopause (Shao, et al., 2012). Considering the results of the previous studies, we can assume that the timing of estrogen therapy is important. The protective effects of pregnancy loss against cognitive impairment and dementia found in this study suggest that estrogen therapy before menopause may have protective effects against cognitive impairment or dementia in old age. Beneficial effects of hormonal contraceptive use on cognitive functions in elderly women reported by Karim et al. (Karim, et al., 2016) support this suggestion. Further study is needed to determine the proper timing for estrogen therapy to have a protective role against dementia.

Although we reported the close relationship between pregnancy loss and childbirth with late life cognition and the risk of dementia, our study has several limitations. Firstly, the results should be considered with regards to the characteristics of the subjects. The association between reproductive experiences and cognition in elderly women may be due to other factors, such as age, education and disease. The elderly women who have experienced a loss of pregnancy were younger and more educated than those who have not experienced a loss of pregnancy, and the multiparous women were older and less educated than the nulli- and primiparous women. Other birth-delivery associated complications or medical conditions may have influenced the late life cognition of the risk of dementia. The number of births was

positively associated with a high BMI (Lao, et al., 2006), type 2 diabetes (Nicholson, et al., 2006) and strokes (Jung, et al., 2010). The spontaneous abortion rate is higher in women with obesity or insulin-dependent diabetes (Cunningham, 2014). Older age, lower education, depression, history of stroke and diabetes mellitus were negatively associated with cognitive functions in this study. However, experiences of childbirth and loss of pregnancy were still closely associated with cognitive functions in elderly when these factors were controlled.

Secondly, information on reproductive factors was collected from self-reports. Among the reproductive factors provided by the participants, recall bias is expected to be the highest for the age of menarche, given the longest interval between the time of menarche and that of the self-report. A study that analyzed the validity of the self-reported age at menarche revealed that 95% of middle aged women reported an age at menarche which differed less than 2.2 years (-2.19 to 2.15 years) from that recorded in adolescence (Cooper, et al., 2006). Had the recall biases existed in the reported information on reproductive history, the association between the reproductive factors and cognitive decline or the risk of dementia could not have been measured correctly.

Thirdly, the current study suggested that the loss of pregnancy may protect against cognitive decline in later life through its' influences on sex hormones. The time (first, second

or third trimester) and the cause (spontaneous or induced) of the pregnancy loss are known to differently influence the hormonal fluctuations. However, we did not examine the information on the pregnancy losses in the current study.

Fourthly, women who were never pregnant, hence did not experience any hormonal changes associated with pregnancy, can be further examined to compare their late life cognitive states with women who have experienced multiple pregnancies. Future studies will be able to further illuminate the influence of reproductive hormonal influences to the late life cognition by carefully investigating the more detailed reproductive histories of the subjects.

The strengths of this study include the involvement of a large community-based study and the control of diverse potential confounders, such as the genetic factor APOE and the extensive analysis on the association between reproductive factors and different types of dementia, including Alzheimer's disease, vascular disease, and other types of dementia. All of the above add to previous findings.

5. Conclusion

This study investigated the impacts of reproductive experiences on cognitive functions and the risk of dementia in elderly women. Childbirth experiences were associated with a declined cognitive function and the increased risk of dementia in elderly women. On the contrary, elderly women who had experienced pregnancy loss had better global cognitive functions and a decreased risk of dementia. These results can be explained by reproductive hormone concentrations, which dramatically change during pregnancy. We propose to apply the results of this study to hormone therapy which may reduce the risk of dementia.

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List of Table

Table 1. Demographic, clinical, and reproductive characteristics

Variable	
Age (years, mean ± SD)	71.37 ± 7.11
50-59 years old (n, %)	14, 0.55
60-69 years old (n, %)	1099, 43.26
70-79 years old (n, %)	1074, 42.28
80 years old or over (n, %)	353, 13.90
Education (years, mean ± SD)	5.67 ± 4.74
0 years (n, %)	642, 25.28
1-6 years (n, %)	1107, 43.58
7 year or more (n, %)	791, 31.14
S-GDS(points, mean ± SD)	5.54 ± 3.71
Diabetes mellitus (n, %)	479, 18.86
Apolipoprotein E ε4 alleles	
0 copy (n, %)	1693, 66.65
1 copy (n, %)	410, 16.14
2 copies (n, %)	12, 0.47
Reproductive factors	
Number of childbirth (mean ± SD)	3.74 ± 1.72
0 to 4 (n, %)	1829, 72.00
5 or more (n, %)	711, 2800
Number of pregnancy loss (mean ± SD)	1.61 ± 1.89
None (n, %)	811, 31.90
1 or more (n, %)	1729, 68.10
Age at the first birth (years, mean ± SD)	24.33 ± 3.57
Age at the last birth (years, mean ± SD)	32.54 ± 4.89
Age at menarche (years, mean ± SD)	16.80 ± 2.24
Age at menopause (years, mean ± SD)	50.09 ± 5.09

SD: Standard deviation, S-GDS: Short Geriatric Depression Scale

Table 2. The relationship between reproductive experiences and neuropsychological test scores using stepwise linear regression analysis

DV	IV	B	SE(B)	Beta	Sig.
MMSE	Education	0.36	0.02	0.41	***
	Age	-0.14	0.01	-0.24	***
	S-GDS	-0.17	0.02	-0.14	***
	Childbirth	-0.25	0.05	-0.10	***
	Pregnancy loss	0.13	0.03	0.06	***
CERAD	Education	1.22	0.05	0.40	***
	Age	-0.70	0.03	-0.34	***
	S-GDS	-0.55	0.06	-0.14	***
	Childbirth	-0.53	0.14	-0.06	***
	Pregnancy loss	0.63	0.11	0.08	***
	Diabetes	-1.33	0.51	-0.04	**

Age, education, diabetes, S-GDS, and the reproductive factors entered as independent variables. B = regression coefficient, SE(B) = standard error of B, b = standardized regression coefficient, Sig = Significant levels, *** denotes $p < 0.001$, ** denotes $p < 0.01$.

Table 3. The relationship between reproductive experiences and risk of dementia using multinominal logistic regression analysis

Variables	Odd ratio (95% CI)	Sig.
Age	1.12 (1.08-1.15)	***
Education	0.98 (0.92-1.03)	NS
Diabetes	1.43 (0.92-2.23)	NS
S-GDS	1.2 (1.14-1.26)	***
Number of Childbirth		
0-4	1.00	
≥ 5	1.62 (1.06-2.47)	**
Number of loss of pregnancy	0.82 (0.70-0.95)	
None	1.00	
1 or more	0.46 (0.31-0.67)	***

* Age, education, history of diabetes mellitus, S-GDS, the number of childbirth, and the number of pregnancy loss entered as independent variables. NS denotes not significant, *** denotes $p < 0.001$, ** denotes $p < 0.01$.

Table 4. The association between reproductive experiences and dementia subtypes using multinominal logistic regression analysis

Reproductive experiences	Odd ratio* (95% confidence interval)					
	Alzheimer's dementia	Sig.	Vascular dementia	Sig.	Other dementia	Sig.
Number of childbirth						
0-4	1.00		1.00		1.00	
≥ 5	1.49 (0.93-2.40)	NS	1.74 (0.43-7.04)	NS	2.72 (0.90-8.18)	NS
Number of pregnancy loss						
None	1.00		1.00		1.00	
1 or more	0.6 (0.38-0.95)	*	0.08 (0.02-0.40)	**	0.36 (0.13-0.99)	*

Age, education, history of diabetes mellitus, S-GDS score, the number of childbirth (categorical; 0 to 4, 5 or more), and the number of pregnancy loss (categorical; none, 1 or more) entered in the model. NS denotes not significant, * denotes $p < 0.05$, ** denotes $p < 0.01$.

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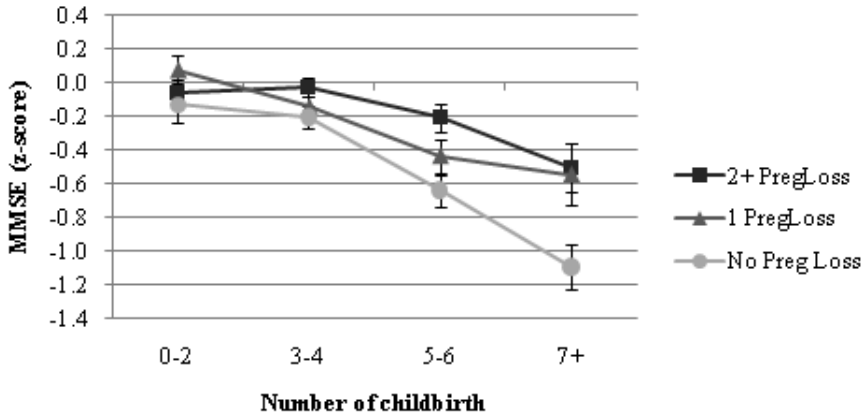
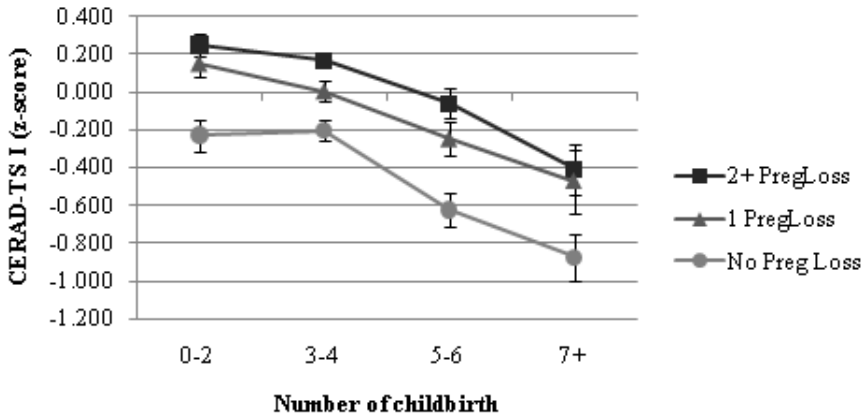
Figure 1. A dose-response relationship of the number of birth on the neuropsychological tests displayed in three groups of elderly women who experienced low to high pregnancy loss

(A)



(B)



(A) Results based on (A) MMSE z-score and (B) CERAD-TS I z-score (controlled for age and education) of the KLOSCAD participants. Error bars represent the standard error.

국문초록

배경: 성호르몬이 뇌와 인지기능에 미치는 영향은 다양한 연구에 의해 증명된 바 있다. 임신 횟수가 노년기 여성의 인지저하나 치매 위험과 관련이 있다는 보고가 있었다. 그러나 임신과 노년기 인지장애와 연관성에 대한 연구 결과는 일관된 결과를 보이지 않았으며, 유산이 미치는 영향에 대해선 연구가 거의 이루어지지 않았다. 임신의 중단, 즉 유산으로 일어나는 성호르몬의 변화는 출산으로 이어지는 정상적인 임신으로 일어나는 성호르몬의 변화와는 차이가 있다.

목적: 본 연구는 유산과 출산이 노년기 여성의 인지저하나 치매 발병에 미치는 영향에 대해 분석하고자 한다.

방법: 본 연구는 한국인의 인지 노화와 치매에 대한 전향적 연구(KLOSCAD)에 참여한 피험자 일부 2,540명을 대상으로 후향적 연구를 시행하였다. 출산관련 경험 자료는 구두보고를 통해 얻어졌다. 체내 호르몬의 영향만 고려하기 위하여 호르몬 대체요법, 자궁절제술 혹은 난소절제술을 시행한 여성들은 분석에서 제외되었다. 전반적 인지능력을 평가하기 위해 Mini Mental State Examination (MMSE)와 Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological assessment battery total score I (CERAD-TS I)가 사용되었다. 치매는 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)에 따라 진단되었으며 경도인지장애(MCI)는 the

consensus criteria from the International Working Group on MCI에 따라 진단되었다.

결과: 출산을 많이 경험한 여성일수록 MMSE 점수와 CERAD TS-I 점수가 낮았으며 ($p < 0.001$), 유산을 많이 경험한 여성일수록 MMSE 점수와 CERAD TS-I 점수가 높았다 ($p < 0.001$). 5회 이상 출산은 유의하게 치매 위험을 상승시켰으며 ($p < 0.01$), 1회 이상의 유산은 치매 위험을 유의하게 낮추었다 ($p < 0.001$). 치매의 원인에 따라 분석하였을 때, 1회 이상의 유산은 알츠하이머성 치매, 혈관성 치매, 그 외 치매유형의 위험을 유의하게 낮추었다.

결론: 본 연구에서 출산과 유산 경험은 노년기 인지능력과 치매 발병률과 근접하게 관련이 있다는 결과를 얻었다. 노년기 인지를 보호하는 출산 관련 호르몬 변화를 모방하여 호르몬대체요법에 적용하면 치매 위험을 낮출 수 있을 것으로 기대된다.

주요어: 출산 관련 요인, 출산, 유산,치매, 인지, 위험인자

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