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| **Supplemental Digital Content 1.** Critical appraisal of included studies for spontaneous POI using the Newcastle-Ottawa Quality Assessment Scale | | | | | | | | |
| **Study ID** | **Selection** | | | | **Comparability** | **Exposure** | | |
| **1. Is case definition adequate?** | **2. Cases** | **3. Selection of Controls** | **4. Definition of controls** | **1. Comparability of cases &controls** | **1. Ascertain-ment of exposure** | **2. Same tests forgroups** | **3. Non-response rate** |
| Bermudez 1993 | \*  yes | - no description | - no description | \*  Normalovarianfunction | - | \* medical record | - notreported | - notreported |
| Hartmann 1997 | \* from  medical records | - Patients at outpatient clinic; not known if consecutive  patients | - healthy volunteers for OC study (cycling women) and hospital controls (postmenopausal) | \*  cycling: regular cycle, normal FSH  menopausal: medical record | \*\*  cycling: age- and BMI-matched  menopausal: BMI- and time since menopause-matched | \* medical record | \* outpatientclinic | - notreported |
| Elias 1997 | \* elevated FSH (notspecified) | - no description | - no description | -  no description of source ("normal control subjects") | \*  Age-matched, no information on BMI | - notdescribedforcontrols | - notreported | - notreported |
| Doldi 1998 | \*  FSH > 25.6 IU/L | - no description | - Hospitalcontrols | \*  medical record | \*\*  Similarageand BMI | \* medical record | \* outpatientclinic | - notreported |
| Falsetti 1999 | \* from  medical records | - no description | - no description | \*  medical record | \* \*  Similarageand BMI | \* medical record | - notreported | - notreported |
| Benetti-Pinto 2005 | \*  from  medical records | - no description | - no description | \*  Control 1: regular menstrual cycle  Control 2: Postmenopausal | \*\*  young controls: matched for age and BMI  menopause controls: matched for duration of amenorrhea | \* medical record | - notreported | - notreported |
| Kalantaridou 2006 | \* from  medical records | \*  Recruitment letters, internet. | \* General population recruitment by advertisement. | \*  medical record | \* \*  Similar age and BMI, adjusted for ethnicity | \* medical record | \* | - notreported |
| Van der Stege 2008 | \* from  medical records | - Invitation, response rate 47% | \* General population recruitment by advertisement | \*  medical record, hormonal screening | \*\*  Adjusted for age and BMI | \* medical record | \* | -  notreported |
| Janse 2011 | \*  from  medical records | \*  consecutivepatientsvisitingoutpatientclinic | -  Hospitalcontrols | \*  medical record, FSH < 12 IU/L | \*\*  Adjusted for age and BMI | \*  medical record | \* | -  notreported |
| Gulhan 2012 | \*  from  medical records | - Patients at outpatient clinic; not known if consecutive  patients | - no description | \*  medical record | \*\*  Similarageand BMI | \*  medical record | \* | -  notreported |
| Ates 2014 | \*  from  medical records | \*  consecutivepatientsvisitingoutpatientclinic | - no description | \*  medical record | \*  Age-matched, no information on BMI | \* medical record | \* | -  notreported |
| Daan 2015 | \*  from  medical records | - Patients at outpatient clinic; not known if consecutive  patients | \*  Included women were participants in a preconceptional cohort study in IVF clinic | \*  Control 1: regular menstrual cycle  Control 2: Postmenopausal | - | \* medical record | \* | -  notreported |
| Szlendak-Sauer  2016 | \*  from  medical records | - no description | - no description | \*  medical record | - | \* medical record | \* | -  notreported |
| Florence 2016 | \*  from  medical records | - Patients at outpatient clinic; not known if consecutive  patients | -  Hospitalcontrols | \*  medical record | \*  Age-matched, no information on BMI | \* medical record | \* | -  not reported |
| Abbreviations: POI: primary ovarian insufficiency; FSH: follicle-stimulating hormone; BMI: body mass index; MP: menopause. | | | | | | | | |
| **Selection** | | | | | | | | |
| 1. Is the case definition adequate? a) yes, with independent validation\* b) yes, e.g. record linkage or based on self reports c) no description | | | | | | | | |
| 2. Representativeness of cases. a) consecutive or obviously representative series of cases\* b) potential for selection biases or not stated | | | | | | | | |
| 3. Selection of controls. a) community controls\* b) hospital controls c) no description | | | | | | | | |
| 4. Definition of controls. a) no history of disease (endpoint)\* b) no description of source | | | | | | | | |
| **Comparability** | | | | | | | | |
| 1. Comparability of cases and controls on the basis of the design or analysis. a) study controls for \_\_(select most important factor)\*. b) study controls for any additional factor\* (this criteria could be modified to indicate specific control for a second important factor) | | | | | | | | |
| **Exposure** | | | | | | | | |
| 1. Ascertainment of exposure. a) secure record (e.g. surgical records)\* b) structured interview where blind to case/control status\* c) interview not blinded to case/control status d) written self report or medical record only e) no description | | | | | | | | |
| 2. Same method of ascertainment for cases and controls. a) yes\* b) no | | | | | | | | |
| 3. Non-Response rate. a) same rate for both groups\* b) non respondents described c) rate different and no designation | | | | | | | | |