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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 | \*frommedical records | -Patients at outpatient clinic; not known if consecutivepatients | -healthy volunteers for OC study (cycling women) and hospital controls (postmenopausal) | \*cycling: regular cycle, normal FSHmenopausal: medical record | \*\*cycling: age- and BMI-matchedmenopausal: 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 | \*frommedical records | -no description | -no description | \*medical record | \* \*Similarageand BMI | \*medical record | -notreported | -notreported  |
| Benetti-Pinto 2005 | \*frommedical records | -no description | -no description | \*Control 1: regular menstrual cycleControl 2: Postmenopausal | \*\*young controls: matched for age and BMImenopause controls: matched for duration of amenorrhea | \*medical record | -notreported | -notreported  |
| Kalantaridou 2006 | \*frommedical 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 | \*frommedical records | -Invitation, response rate 47% | \*General population recruitment by advertisement | \*medical record, hormonal screening | \*\*Adjusted for age and BMI | \*medical record | \* | -notreported  |
| Janse 2011 | \*frommedical records | \*consecutivepatientsvisitingoutpatientclinic | -Hospitalcontrols | \*medical record, FSH < 12 IU/L | \*\*Adjusted for age and BMI | \*medical record | \* | -notreported |
| Gulhan 2012 | \*frommedical records | -Patients at outpatient clinic; not known if consecutivepatients | -no description | \*medical record | \*\*Similarageand BMI | \*medical record | \* | -notreported |
| Ates 2014 | \*frommedical records | \*consecutivepatientsvisitingoutpatientclinic | -no description | \*medical record | \*Age-matched, no information on BMI | \*medical record | \* | -notreported |
| Daan 2015 | \*frommedical records | -Patients at outpatient clinic; not known if consecutivepatients | \*Included women were participants in a preconceptional cohort study in IVF clinic | \*Control 1: regular menstrual cycleControl 2: Postmenopausal | - | \*medical record | \* | -notreported |
| Szlendak-Sauer2016 | \*frommedical records | -no description | -no description | \*medical record | - | \*medical record | \* | -notreported |
| Florence 2016 | \*frommedical records | -Patients at outpatient clinic; not known if consecutivepatients | -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 |