Supplementary material

Full search strategy for MEDLINE/PubMed

We searched MEDLINE/PubMed on the 26th of May 2015 with the following Medical Subject Heading (MeSH) terms combined as below:

("Fertility"[Mesh] OR "Infertility, Female"[Mesh] OR "Reproduction"[Mesh] OR "Preconception Care"[Mesh]) OR ("Reproductive Techniques, Assisted"[Mesh]) OR "Reproductive Techniques"[Mesh]) AND ("Caffeine/adverse effects"[Mesh] OR "Coffee"[Mesh]) AND ("Case-Control Studies"[Mesh]) OR "Cohort Studies"[Mesh])

Also, a supplementary search was conducted with free text terms in order to include non-indexed new literature.
((((((coffee) OR "Coffee"[Mesh])) OR ((((caffeine) OR "Caffeine"[Mesh])) AND "adverse effects" [Subheading]))) AND ((((((("Reproductive Techniques"[Mesh]) OR "Reproductive Techniques, Assisted"[Mesh]) OR "fertility treatment") OR "Fertility"[Mesh]) OR "Infertility, Female"[Mesh]) OR "Reproduction"[Mesh]) OR "Preconception Care"[Mesh])) AND ((((((("Pregnancy Rate") OR "Pregnancy Rate"[Mesh])) OR (("Birth Rate") OR "Birth Rate"[Mesh])) OR (miscarriage OR "Spontaneous abortion" OR "Abortion, Spontaneous"[Mesh])) OR (("Time-to-Pregnancy") OR "Time-to-Pregnancy"[Mesh]))

The search was limited to humans and restricted to published data. No restrictions were made according to language or publication period.

The search was repeated on the 3th of April 17 – one new article was added to the review

Data extraction form for systematic review

"The effects of coffee and caffeine consumption on fecundity and fertility: A systematic review and meta-analysis"

Article data:

Firtst Author surname	
Title	
Country	
Year of publication and journal	

Article content:

Study design		
Study population (size and selection)	Study enrollment;	
Inclusion criteria (selection)		
Exclusion criteria		
Assessment of intake (X)		Prospective (before conception/SAB)
		Retrospective
Methode of assessment of exposure (X)		Questionaires
		Interview
		Blodsamples
Assessment of exposure/caffeine (X)		Based on total/multiple dietary factors
		Based just on coffee
Assessment of outcome		
Confounder control		
Results		

Conclusion:

Effect – estimate (X)	
Nonsignificant effect (X)	

Limitations (X)		Small sample size
		Selection bias
		Information bias
		Confounding

Quality scoring (NOS)

Selection				Comparability		Exposure (CC) or Outcome (Cohort)		
1	2	3	4	1		1	2	3

NOS explanatory form

1) **Cohort studies**

Selection

- 1) a * is awarded if the exposed cohort is a) "truly representative" or b) "somewhat representative" of the average coffee drinking women of the fertile age.
  Obs. "volunteers" does NOT mean volunteering/accepting to participate in a well-defined study. Volunteering would be the case for instance if participants answered an add in the newspaper.
- 4) Both in the case of prospectively and retrospectively collected data a * is only awarded if a viable pregnancy is demonstrated at the time of the interview by either 2 consecutive increased hCG-tests or a positive ultrasound.

Comparability

- 1) either adjustment or stratification is considered adequate for awarding a *

Outcome

- 1) Most fecundability studies rely on self-report → will not be awarded a *
- 3)
  b) subjects lost to follow up > 80% i.e. if > 80% of eligible women are included and followed or description provided of those lost, a * is awarded
  c) if <80% of eligible women are included and no description of those lost
  d) if no statement of number or % of eligible women is provided

2) **Case-control studies**

Selection

- 1) "independent validation" i.e. 1) data from medical records or 2) self-reports subsequently validated by checking e.g. medical records, is awarded a *
- 2) "obviously representative series of cases" – if cases are obviously selected e.g. women with diabetes, the study will NOT be awarded a *. Also if the eligible number of women is not known, a * will NOT be awarded.
- 3) - "community controls" equals uncomplicated pregnancies (i.e. pregnancies without experiencing SAB at the point of data collection) - most women are involved with hospital facilities at some point during pregnancy, but this does not label them "hospital controls"
- 4) if controls are pregnant women with normal deliveries they can per se not have the outcome/SAB and in that case a * will be awarded

Comparability

- 1) Either adjustment (including matching) or stratification is considered adequate for awarding a *

Exposure

- 1 b)* if awarded a * it must be explicitly stated that the interviewer(s) were blinded to case/control status

Elaborated reasons for exclusion

Medline + Embase search:
- The computerized literature search resulted n=378 citations
  (Medline: n=140 and Embase: n=238)
- Duplicates in the two databases, n=90
- Repeated database search, n=1
- From Medline and Embase search in total included, **n= 289**

Reference list search:
- Potential unique citations n=68
- Duplicates (i.e. included in the search from Medline and Embase), n=46
- From search in reference lists in total included**, n=21**

Total number of unique records identified, n=311

Exclusion of non-relevant records based on title and abstract, n=195

Unique full-text articles assessed for eligibility, n=116

Full-text articles excluded due to, n=68;
- reporting exposure assessment after outcome (Stanton et al. 1995[1]; Hatch et al. 1993[2]; Williams et al. 1990[3]), n=3

- not clearly stating whether exposure information refers to the time-period before or after the outcome occurred, (we have tried to contact the authors but either the contact information was not valid or the authors did not reply on our request)
(Curtis et al. 1997[4]; Hansteen et al. 1990[5]; Joesoef et al. 1990[6]; Hassan et al. 2004[7]; Weathersbee et al. 1977[8]), n=5

- not reporting the outcome of interest. Instead reporting; fetal dead (Matijasevich et al. 2006[9]), stillbirth (Wisborg et al. 2003[10]), "SAB" > gestational week 24(=stillbirth) (Furuhashi et al. 1985[11]), ovulatory disorder infertility (Chavarro et al. 2009[12]) + others (Grodstein et al. 1993[13]), n=5

- not reporting exposure as caffeine/cups of coffee, but instead reporting s-paraxanthine (Klebanoff et al. 1999[14]), coffee and tea together without an numerical coffee value (Huang et al. 2012[15]) or only caffeine from the medication letigen (Howards et al. 2012[16]) n=3

- not reporting an exposure of interest (Ferreira et al. 2010[17]; Halpern et al. 2010[18]; Anderson et al. 2009[19]; Killick et al. 2009[20]; Taylor et al. 2009[21]; Karypidis et al. 2006[22]; Fenster et al. 1998[23]), n=7

- not reporting an effect estimate and not providing data for us to calculate an effect estimate (Watkinson et al. 1985[24]; Tebbutt et al. 1984[25]), n=2

- reporting stratified results using data from the study by Cnattingies et al. 2000 = replication of data in another publication (Signorello et al. 2001[26]) + (Agnesi et al. 2003[27]), n=2

- review (Lassi et al. 2014[28]; Rooney et al. 2014[29]; Gupta et al. 2013[30]; Morgan et al. 2013[31]; Mmbaga et al. 2012[32]; Heidaryfard et al. 2012[33]; Brent et al. 2011[34]; Sadeu et al. 2010[35]; Kuczkowski et al. 2009[36]; Scott et al. 2009[37]; Signorello et al. 2004[38]; Nawrot et al. 2003[39]; Christian et al. 2001[40]; Hinds et al. 1996[41]; Narod et al. 1991[42]; Leviton et al 1988[43]; Heller et al. 1987[44]), n=17

- reporting replies (Kuczkowski et al. 2010[45]; Graham et al. 2008[46]; Lynch et al. 2008[47]; Signorello et al. 2008[48]; Armstrong et al. 2008[49]; Chura et al. 2007[50]; Lawson et al. 2004[51]; Cnattingius et al. 2003[52]; Olsen et al. 2001[53]; Gilbert-Barness et al. 2000[54]; Jester et al. 2000[55]; Eskenazi et al. 1999[56]; Robertson et al. 1998[57]; Parazzini et al. 1994[58]; Kline et al. 1994[59]; Wei et al. 1994[60]; Fenster et al. 1991[61]; Stein et al. 1991[62]), n=18

- only available abstract and not full text article (Nouri et al. 2013[63]; Kesmodel et al. 2012[64]; Pauli et al. 2010[65]; Imaz et al. 2009[66]; Gilbert et al. 2008[67]), n=5

- article not available from Nordic libraries (Hruba et al. 1997[68]), n=1

Excluded from the review after assessing data-quality, n=1
- Spinelli et al. 1997[69] – not reporting sufficient data for inclusion in the meta-analysis AND when trying to calculate crude OR based on numbers from the article, the results becomes remarkably different as compared with the crude OR reported in the article – thus, we cannot be sure which estimates to believe in and thus the study has to be excluded from the review in general

Studies included in the review, n=47

Studies excluded from the meta-analysis (n=12)
- Due to not reporting sufficient information on number of cases and/or number of subjects and not replying sufficiently on mail correspondence
Fecundity studies (Wilcox et al. 1988[70]; Christianson et al. 1989[71]; Florack et al. 1994[72]; Bolumar et al. 1997[73]; Jensen et al. 1998[74]; Pollack et al. 2010[75]; Taylor et al. 2011[76]), n=7
SAB studies (Axelsson et al. 1989[77]; Stefanidou et al. 2011[78]), n=2

- Due to not reporting more than two estimates (the reference group and only one additional estimate) and thus not being able to contribute to a dose-response meta-analysis (Parazzini et al. 1991[79]; Lubna et al. 1994[80]; Khoury et al. 2004[81]), n=3

Studies included in the meta-analysis, n=35

Table S1a – Characteristics and risk of bias table for publications on coffee/caffeine and fecundity

Author and year	Country	Design	Source of caffeine	Risk of bias			
				Selection	Comparability	Exposure/outcome	Total NOS-score
Wilcox et al. 1988[70]	US	Cohort	Multiple	**	**	**	6
Christianson et al. 1989[71]	US	Cohort	Coffee	**	*	*	4
Olsen et al. 1991[82]	Denmark	Cohort	Multiple	**	**	**	6
Florack et al. 1994[72]	Netherlands	Cohort	Coffee	****	*	**	7
Alderete et al. 1995[83]	US	Cohort	Coffee	***	**	**	7
Bolúmar et al. 1997[73]	Spain	Cohort	Multiple	***	**	*	6
Caan et al. 1998[84]	US	Cohort	Multiple /Coffee	**	**	**	6
Hakim et al. 1998[85]	US	Cohort	Coffee	***	**	**	7
Jensen et al. 1998[74]	Denmark	Cohort	Multiple /Coffee	***	*	*	5
Pollack et al. 2010[75]	US	Cohort	Multiple	***	**	**	7
Taylor et al. 2011[76]	US	Cohort	Multiple	***	**	*	6
Hatch et al. 2012[86]	US	Cohort	Multiple /Coffee	***	**	*	6

In each category (i.e. selection, comparability and exposure/outcome) a range of cero to three * could be awarded. The maximum total NOS-score is 9.

Table S1b – Characteristics and risk of bias table for publications on caffeine and spontaneous abortion (SAB)

Author and year	Country	Design	Source of caffeine		Risk of bias			
					selection	comparability	Expsure/outcome	Total NOS-score
Srisuphan et al. 1986[87]	US	Cohort	Multiple		***	*	**	6
Axelsson et al. 1989[77]	Sweden	Cohort	Coffee		*	*	***	5
Wilcox et al. 1990[88]	US	Cohort	Multiple		***	*	**	6
Fenster et al. 1991[89]	US	Case-control	Multiple		***	**	**	7
Kline et al. 1991[90]	US	Case-control	Multiple		***	*	**	6
Parazzini et al. 1991[79]	Italy	Case-control	Coffee		****	*	*	6
Armstrong et al. 1992[91]	US	Cohort	Coffee		***	**	*	6
Infante-Rivard et al. 1993[92]	Canada	Case-control	Coffee		****	**	*	7
Mills et al. 1993[93]	US	Cohort	Multiple		***	**	***	8
Dominguez-Rojas et al. 1994[94]	Spain	Cohort	Coffee		**	*	**	5
Lubna et al. 1994[80]	Saudi Arabia	Case-control	Multiple		****		*	5
Dlugosz et al. 1996[95]	US	Cohort	Multiple /Coffee		***	**	***	8
Zhang et al. 1996[96]	US	Cohort	Coffee		**		*	3
Agnesi et al. 1997[97]	Italy	Case-control	Coffee		***	**	*	6
Fenster et al. 1997[98]	US	Cohort	Multiple		**	**	***	7
Parazzini et al. 1998[99]	Italy	Case-control	Coffee		****	**	**	8
Cnattingius et al. 2000[100]	Sweden	Case-control	Multiple		****	**	**	8
Wen et al. 2001[101]	US	Cohort	Multiple		*		**	3
Giannelli et al. 2003[102]	UK	Case-control	Multiple		***	*	**	6
Rasch et al. 2003[103]	Denmark	Case-control	Multiple		****	**	**	8
Tolstrup et al. 2003[104]	Denmark	Case-control	Multiple		***	**	*	6

Khoury et al. 2004[81]	US	Cohort	Multiple		**	*	*	4
Bech et al. 2005[105]	Denmark	Cohort	Coffee		***	**	**	7
Sata et al. 2005[106]	Japan	Case-control	Multiple		***	*	**	6
George et al. 2006[107]	Sweden	Case-control	Multiple		****	**	**	8
Maconochie et al. 2007[108]	UK	Case-control	Multiple		***	*	*	5
Savitz et al. 2008[109]	US	Cohort	Multiple /Coffee		***	**	***	8
Weng et al. 2008[110]	US	Cohort	Multiple /Coffee		***	**	*	6
Agnesi et al. 2010[111]	Italy	Case-control	Coffee		***	*	*	5
Greenwood et al. 2010[112]	UK	Cohort	Multiple /Coffee		***	**	***	8
Pollack et al. 2010[75]	US	Cohort	Coffee		***	**	*	6
Stefanidou et al. 2011[78]	Italy	Case-control	Multiple		****	**	*	7
Hanh et al. 2015[113]	Denmark	Cohort	Multiple /Coffee		**	**	***	7

In each category (i.e. selection, comparability and exposure/outcome) a range of cero to three * could be awarded. The maximum total NOS-score is 9.

Table S1c – Characteristics and risk of bias table for publications on caffeine and Medically Assisted Reproduction (MAR)

Author and year	Country	Design	Source of caffeine		Risk of bias			
					Selection	Comparability	Exposure/outcome	Total NOS-score
Klonoff-Cohen et al. 2002[114]	US	Cohort	Multiple		***	**	**	7
Iman Al-Saleh et al. 2010[115]	Saudi Arabia	Cohort	Multiple /Coffee		***	**	**	7
Choi et al. 2011[116]	US	Cohort	Multiple		***	**	**	7

In each category (i.e. selection, comparability and exposure/outcome) a range of cero to three * could be awarded. The maximum total NOS-score is 9.

1. Stanton CK, Gray RH. Effects of caffeine consumption on delayed conception. 1995(0002-9262 (Print)).
2. Hatch EE, Bracken MB. Association of delayed conception with caffeine consumption. *American Journal of Epidemiology.* 1993;138(12):1082-1092.
3. Williams MA, Monson RR, Goldman MB, Mittendorf R, Ryan KJ. Coffee and delayed conception. *Lancet.* 1990;335(8705):1603.
4. Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. Vol 1461997:32-41.
5. Hansteen IL. Occupational and lifestyle factors and chromosomal aberrations of spontaneous abortions. 1990(0361-7742 (Print)).
6. Joesoef MR, Beral V, Rolfs RT, Aral SO, Cramer DW. Are caffeinated beverages risk factors for delayed conception? *Lancet.* 1990;335(8682):136-137.
7. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. 2004(0015-0282 (Print)).
8. Weathersbee Ps Fau - Olsen LK, Olsen Lk Fau - Lodge JR, Lodge JR. Caffeine and pregnancy. A retrospective survey. 1977(0032-5481 (Print)).
9. Matijasevich A, Barros FC, Santos IS, Yemini A. Maternal caffeine consumption and fetal death: a case-control study in Uruguay. *Paediatr Perinat Epidemiol.* 2006;20(2):100-109.
10. Wisborg K, Kesmodel U, Bech BH, Hedegaard M, Henriksen TB. Maternal consumption of coffee during pregnancy and stillbirth and infant death in first year of life: prospective study. *BMJ.* 2003;326(7386):420.
11. Furuhashi NS, S.; Suzuki, M.; Hiruta, M.; Tanaka, M.; Takahashi, T. Effects of caffeine ingestion during pregnancy. 1985(0378-7346 (Print)).

12. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Caffeinated and alcoholic beverage intake in relation to ovulatory disorder infertility. Vol 202009:374-381.
13. Grodstein F, Goldman MB, Ryan L, Cramer DW. Relation of female infertility to consumption of caffeinated beverages. *American Journal of Epidemiology.* 1993;137(12):1353-1360.
14. Klebanoff MA, Levine Rj Fau - DerSimonian R, DerSimonian R Fau - Clemens JD, Clemens Jd Fau - Wilkins DG, Wilkins DG. Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. 1999(0028-4793 (Print)).
15. Huang H, Hansen Kr Fau - Factor-Litvak P, Factor-Litvak P Fau - Carson SA, et al. Predictors of pregnancy and live birth after insemination in couples with unexplained or male-factor infertility. 2012(1556-5653 (Electronic)).
16. Howards PP, Hertz-Picciotto I, Bech BH, et al. Spontaneous abortion and a diet drug containing caffeine and ephedrine: a study within the Danish national birth cohort. *PLoS One.* 2012;7(11):e50372.
17. Ferreira RC, Halpern G, Figueira Rde C, Braga DP, Iaconelli A, Jr., Borges E, Jr. Physical activity, obesity and eating habits can influence assisted reproduction outcomes. *Womens Health (Lond).* 2010;6(4):517-524.
18. Halpern G, Ferreira RC, Braga DPAF, et al. Lifestyle factors and eating habits influence on intracytoplasmic sperm injection cyles outcomes. *Journal of Reproductionmedizin und Endokrinologie.* 2010;7:4:287.
19. Anderson BL, Juliano LM, Schulkin J. Caffeine's implications for women's health and survey of obstetrician-gynecologists' caffeine knowledge and assessment practices. *J Womens Health (Larchmt).* 2009;18(9):1457-1466.
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21. Taylor KC, Murray LE, Small CM, et al. NAT2 haplotypes modify the effects of smoking, alcohol, and caffeine on fertility *Genetic Epidemiology* 2009;33:8:776.
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(0724-438X (Print)).
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27. Agnesi R, Valentini F, Meneghetti M, et al. [Changes in risk factors for spontaneous abortion in an area with high concentrations of shoe manufacture after a preventive intervention]. *G Ital Med Lav Ergon.* 2003;25 Suppl(3):79-80.

28. Lassi ZS, Imam AM, Dean SV, Bhutta ZA. Preconception care: caffeine, smoking, alcohol, drugs and other environmental chemical/radiation exposure. *Reprod Health.* 2014;11 Suppl 3:S6.
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