Table 4: Evidence table – Hogen Esch et al. (2011)

Study type	Retrospective case series (with historical control)
Country	Netherlands
Number of patients	N=1038 male-female couples (N=2076 individuals)
quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? Yes 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Na 7. What are the results? No relationship between CD and subfertility 8. How precise are the results? Imprecise wide CI 9. Do you believe the results? Not clear

<table>
<tr><td></td><td>10. Can the results be applied to the local population? Yes
11. Do the results fit with other available evidence? Yes
12. What are the implications of this study for practice? Nil</td></tr>
<tr><td>Study population</td><td>Couples who visited the fertility clinic of the Leiden University Medical Centre bewteen 2003 and 2009; blood samples which were saved for each individual for 10 years were kept for the purposes of checking for sexually transmitted diseases; none had previouslydiagnosed CD

Exclusion: couples in which there was no serum available to test (Of 1180 couples available, 142 did not have serum to test so 1038 couples were included [88%]).

Patient characteristics (n=1038)
<table>
<tr><td></td><td>Females</td><td>Males</td></tr>
<tr><td>Medan age (range)</td><td>32.3 (20-45)</td><td>35.4 (20-64)</td></tr>
<tr><td>Median BMI in kg/m^2 (range)[a]</td><td>N=798 23.3 (16-49)</td><td>N=590 25.4 (18-48)</td></tr>
</table>
[a] BMI not measured in all

Prevalence by causes of subfertility:
(69% of those included were examined for primary subfertility and 31% for secondary subfertility)
<table>
<tr><td></td><td colspan="2">Study group (n=2076)</td><td colspan="2">Unrecognised CD (seropositive) (n=10)</td></tr>
<tr><td></td><td>Females (n=1038)</td><td>Males (n=1038)</td><td>Females (n=6)</td><td>Males (n=4)</td></tr>
<tr><td>Ovulation disorder</td><td>20% (203)</td><td>n/a</td><td>1.48% (3)</td><td>n/a</td></tr>
<tr><td>Tubal factor</td><td>10% (100)</td><td>n/a</td><td>0</td><td>n/a</td></tr>
<tr><td>Male factor</td><td>n/a</td><td>45% (464)</td><td>n/a</td><td>0.22% (1)</td></tr>
<tr><td>Partners of subject with particular subfertility diagnosis</td><td>37% (384)</td><td>22% (223)</td><td>0.26% (1)</td><td>0.45% (1)</td></tr>
<tr><td>Unexplained</td><td>34% (351)</td><td>34% (351)</td><td>0.57% (2)</td><td>0.57% (2)</td></tr>
</table></td></tr>
<tr><td>Control</td><td>Rate of unrecognised CD was compared in the study participants to those in the general population (from a published screening study from the same authors)</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
</table>

Details of coeliac testing

IgA anti-tTG type 2 (ELIA™ Celikey® assay at the Immunocap® 250 system using human recombinnant tissues transglutaminase as an antigen, Phadia GmbH, Freiburg, Germany; >10 U/mL is positive and 7-10 U/mL is equivocal area)
IgA EMA using monkey's oesophagus as substrate (dilution1:10) according to manufacturer (Scimedx)

Unrecognised CD was defined if tests results for both were positive in one subject. (authors stated that this accurately predicts the presence of subtotal villous atrophy) (small bowel biopsies were not offered to the subjects)

(control subjects were tested similarly but for IgA anti-TG2 using a guinea pig substrated from in house developed ELISA)

Results

12 samples had positive IgA anti-TG2 levels considered positive for CD (0.6%; median 60 U/ml, range 13-137)
IgA-EMA was positive in 10/12 of those positive for IgA anti-TG2 (83%)

Prevalence of unrecognised CD (defined as seropositivity)	Study group of subfertile couples	Control group [a]	OR (95% CI) [b]
Overall	**0.48% (10/2076) of individuals [c]**	**0.35% (5/1432)**	**1.38 (0.471, 4.05)**
In females	0.58% (6/1038)	0.28% (2/716)	2.08 (0.42, 10.31)
In males	0.39% (4/1038)	0.42% (3/716)	0.92 (0.21, 4.12)
Females with unexplained subfertility in females	0.57% (2/351)	0.28% (2/716)	2.05 (0.29, 14.58)
Males with unexplained subfertility	0.57% (2/351)	0.42% (3/716)	1.35 (0.23, 8.19)
Females with an ovulation disorder	1.48% (3/203)	0.28% (2/716)	5.36 (0.89, 32.27)
Subfertility due to male factor	0.22% (1/464)	0.42% (3/716)	0.51 (0.05, 4.95)

[a] from previous study described above under 'control', [b] Fisher's exact test, [c] in no couples did both partners have unrecognised CD

Of the 10 subjects in the study group with unrecognised CD:

	Females (n=6)	Males (n=4)	Significance
Mean age (SD)	29 (±5.3)	36 (±3.1)	NS
Mean BMI in kg/m^2 (range)[a]	N=4 25.4 (±2.9)	N=2 24.5 (±0)	NS

[a] BMI not measured in all

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Conflicts of interest

Not reported

Comments

Definitions of abbreviations are given at the end of this document.