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Clinical relevance of genetic variants of gonadotrophins and their receptors in controlled ovarian stimulation: a systematic review and meta-analysis

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BACKGROUND: Genotype has been implicated in the outcome of ovarian stimulation. The analysis of patient-specific genotypes might lead to an individualized pharmacogenomic approach to controlled ovarian stimulation (COS). However, the validity of such an approach remains to be established.

OBJECTIVE AND RATIONALE: To define the impact of specific genotype profiles of follicle-stimulating hormone, luteinizing hormone and their receptors (FSHR, LHR and LHCGR) on ovarian stimulation outcome. Specifically, our aim was to identify polymorphisms that could be useful in clinical practice, and those that need further clinical investigation.

SEARCH METHODS: A systematic review followed by a meta-analysis was performed according to the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines without time restriction. We searched the PubMed/MEDLINE, Cochrane Library, SCOPUS and EMBASE databases to identify all relevant studies published before January 2017. Only clinical trials published as full-text articles in peer-reviewed journals were included. The primary outcome was the number of oocytes retrieved.

OUTCOMES: Fifty-seven studies were assessed for eligibility, 33 of which were included in the qualitative and quantitative analyses. Data were independently extracted using quality indicators. COS outcomes related to seven polymorphisms (*FSHR* [rs6165], *FSHR* [rs6166], *FSHR* [rs1394205], *LHB* [rs1800447], *LHB* [rs1056917], *LHCGR* [rs2293275] and *LHCGR* [rs13405728]) were evaluated. More oocytes were retrieved from *FSHR* (rs6165) AA homozygotes (five studies, 677 patients, weighted mean difference [WMD]: 1.85, 95% CI: 0.85–2.85, $P < 0.001$; $I^2 = 0\%$) than from GG homozygotes and AG heterozygotes (four studies, 630 patients, WMD: 1.62, 95% CI: 0.28–2.95, $P = 0.020$; $I^2 = 56\%$). Moreover, stimulation duration was shorter in *FSHR* (rs6165) AA homozygotes than in AG carriers (three studies, 588 patients, WMD −0.48, 95% CI: −0.87 to −0.10, $P = 0.010$, $I^2 = 44\%$). A higher number of oocytes (21 studies, 2632 patients WMD: 0.84, 95% CI: 0.19 to 1.49, $P = 0.01$, $I^2 = 76\%$) and metaphase II oocytes (five studies, 608 patients, WMD: 1.03, 95% CI: 0.01–2.05, $P = 0.050$, $I^2 = 0\%$) was observed in AA than in GG homozygote carriers. FSH consumption was significantly lower in *FSHR* (rs1394205) GG homozygotes (three studies, 411 patients, WMD: −1294.61 IU, 95% CI: −593.08 to −1996.14 IU, $P = 0.0003$, $I^2 = 99\%$) and AG heterozygotes (three studies, 367 patients, WMD: −1014.36 IU, 95% CI: −364.11 to −1664.61 IU, $P = 0.002$, $I^2 = 99\%$) than in AA homozygotes.

WIDER IMPLICATIONS: These results support the clinical relevance of specific genotype profiles on reproductive outcome. Further studies are required to determine their application in a pharmacogenomic approach to ovarian stimulation.

Key words: assisted reproduction / ovarian stimulation / polymorphisms / FSH / gonadotrophins / LH / pharmacogenomics

Introduction

Ideally, a tailored approach to controlled ovarian stimulation (COS) in infertile patients would involve a comprehensive evaluation of the patient's characteristics, including genotype profile. Pharmacogenomics evaluates how genes influence individual responses to medication. Pharmacogenomic approaches appeared to be a cost-effective strategy in several medical fields (Patel *et al.*, 2014; Mizzi *et al.*, 2016). Data regarding the clinical utility of pharmacogenomics in ART are still scanty (Greb *et al.*, 2005). Nonetheless, increasing evidence indicates that specific genetic characteristics of gonadotrophins and their receptors could influence the ovarian response to exogenous gonadotrophins. Specifically, a common single nucleotide polymorphism (SNP) of the FSH receptor (*FSHR*, rs6166) has been associated with increased FSH consumption during COS (Yao *et al.*, 2011). It has also been associated with increased basal levels of FSH, which suggests an impaired response to both endogenous and exogenous gonadotrophins (Perez Mayorga *et al.*, 2000; Behre *et al.*, 2005; Simoni and Casarini, 2014; Alviggi *et al.*, 2016a). Moreover, a *FSHR* polymorphism at position −29 (*FSHR*, rs1394205) was found to be associated with a poor ovarian response (Achrekar *et al.*, 2009b). Similarly, a suboptimal response to IVF was observed in SNP carriers of the gene encoding the LH beta subunit (Alviggi *et al.*, 2011, 2013). Recently, LH receptor SNPs (*LHCGR*, rs2293275 and *LHCGR*, rs12470652) were reported to affect COS and ART (O'brien *et al.*, 2013; Lindgren *et al.*, 2016; Alviggi *et al.*, 2016b). These findings prompted the hypothesis that a 'hypo-response' to gonadotrophin therapy could be related to specific genotype characteristics (Alviggi *et al.*, 2016a). Contrary to poor-responders, 'hypo-responders' have a good prognosis for ART in terms of basal characteristics and ovarian reserve, but require a higher-than-expected dose of gonadotrophins and more prolonged stimulation to obtain an adequate number of oocytes (Alviggi *et al.*, 2013).

Given the steady increase in evidence that SNPs affect COS and ART outcomes, we conducted a systematic review and meta-analysis data in the attempt to summarize the clinical evidence regarding the impact of polymorphisms of gonadotrophins and their receptors on the outcome of COS.

Methods

Protocol and registration

This study was exempt from institutional review board approval because it did not involve human intervention. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis and provide its checklist in the Supplementary material. The study protocol was registered at http://www.crd.york.ac.uk/PROSPERO/ (registration number CRD42016050402) on 31 October 2016, before starting the review process.

Eligibility criteria

We used the PICO (Patients, Intervention, Comparison and Outcomes) model to select our study population. We included only women who underwent COS, and evaluated COS outcomes according to individual genotype expression (Supplementary Table I).

Search strategy

We conducted a systematic search using the MEDLINE (PubMed), EMBASE, SCOPUS and Cochrane Library databases to identify all relevant studies published before January 2017. Combinations of the following keywords and MESH search terms were used: 'COH', 'COS', 'controlled ovarian stimulation', 'ART', 'IVF', 'ICSI', 'FIVET', 'IUI', 'intrauterine insemination', 'ovulation induction', 'polymorphism' OR 'SNP' 'luteinizing hormone/choriogonadotropin receptor' 'LHCGR', 'FSH Receptor', 'FSHR', 'FSH', 'follicle-stimulating hormone', 'follicle-stimulating hormone, beta subunit', LH', 'luteinizing hormone' and 'luteinizing hormone, beta subunit'. No time or language restrictions were adopted, and queries were limited to human studies. The reference lists of relevant reviews and articles were also hand-searched.

Selection of studies

Two reviewers (A.C. and D.S.) independently evaluated titles and abstracts. Duplications were removed using Endnote online software and manually. Disagreements were resolved by discussion among authors, and if required, with the involvement of the most experienced authors (C.A., S.E., C.Y.A, P.H, G.D. and M.S). Only clinical trials published in peer-reviewed journals were evaluated. Case series, case reports, book chapters, congress abstracts and gray literature were not included.

Data extraction

Data were extracted independently by two reviewers (A.C. and D.S.) using predefined data fields, and study quality indicators. Discrepancies were resolved by discussion with the senior authors (C.A., S.E., C.Y.A., P.H, G.D. and M.S.).

Risk of bias, summary measures and synthesis of the results

The risk of bias and the quality of the studies included in this meta-analysis were evaluated. Two authors (A.C. and D.S.) independently assessed the risk bias of each study. The senior authors (C.A., S.E., C.Y.A., P.H., G.D. and M.S.) resolved conflicts. The Newcastle–Ottawa scale (NOS) score was used to evaluate the studies included, and judgment on each one was passed according to three issues: selection of the study group, comparability between groups and ascertainment of exposed/not exposed cohorts (Wells *et al.*, 2004).

The primary outcome was the number of oocytes retrieved. Secondary outcomes were: FSH consumption, stimulation duration (number of days of gonadotrophin use for COS), the number of metaphase II (MII) oocytes and ongoing pregnancy rate (OPR). OPR was defined as a pregnancy diagnosed by ultrasonographic visualization of at least one gestational sac. Bias across studies regarding the primary outcome was assessed using visual inspection of funnel plots, the trim and fill method (Duval, 2006) and the Egger test (Egger *et al.*, 1997).

Quantitative analysis

Statistical analysis was carried out using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration). Categorical data were combined with a pooled odds ratio (OR) using the Mantel–Haenszel method. Continuous data were combined with weighted mean difference (WMD) using the inverse variance method. When at least three studies were available, a meta-analysis was conducted using the fixed-effect model. The random-effect model was used in case of significant heterogeneity among studies. Heterogeneity was assessed using the percentage of total variation in the estimated effect across studies (I^2). An I^2 value > 50% indicates substantial heterogeneity. *P*-values <0.05 were considered statistically significant. We applied Bonferroni correction in case of statistical significance. Subgroup analysis by type of exogenous FSH (i.e. recombinant versus urinary) was conducted to assess potential sources of heterogeneity in the number of oocytes retrieved. We also evaluated differences in FSH basal level in relation to *FSHR* 919 G>A (rs6165) and *FSHR* 2039 G>A (rs6166) genotype distribution. Sensitivity analysis was carried out to assess the leverage of studies with a low risk of bias (NOS ≥ 6) on the results. For the primary outcome, an additive effect of genotypes was also tested. Using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria), we estimated Hedges' g and the corresponding SE for each study adopting a simulation approach based on a linear regression model (John *et al.*, 2018). In detail, to test the additive model pooled Hedges' g was computed with a fixed-effect model or random-effect model in case of significant heterogeneity among studies.

Results

Study selection and study characteristics

A total of 1051 items were identified (Fig. 1). After removing 167 duplicates using Endnote software (EndNote X 6.0.1, Thomson Reuters, USA, California State University) and 45 duplicates manually, the titles and abstracts of 839 paper were scrutinized. The reference lists of relevant reviews were hand-searched. Fifty-nine articles were assessed for eligibility. Fifteen articles were excluded because they did not fulfill the inclusion criteria. Data extraction was not possible in the case of 10 articles (Daelemans *et al.*, 2004; De Castro *et al.*, 2004; D'alva *et al.*, 2005; Livshyts *et al.*, 2009; Lazaros *et al.*, 2012; Boudjenah *et al.*, 2014; Colognato *et al.*, 2014; Almawi *et al.*, 2015; Laisk-Podar *et al.*, 2015; Valkenburg *et al.*, 2015), because COS and ART were not evaluated in relation to polymorphism genotype expression. Data duplication was detected in studies by Desai *et al.* (2011, 2013) and by Mohiyiddeen and collaborators (Mohiyiddeen *et al.*, 2013a; 2013b). Of these, we included two studies in our analysis (Desai *et al.*, 2011; Mohiyiddeen *et al.*, 2013b). We extracted data regarding MII oocytes from the Mohiyiddeen *et al.* (2013a) study that were not reported in their subsequent paper (Mohiyiddeen *et al.*, 2013b). Thirty-three studies were included in our quantitative and qualitative analysis (Fig. 1 and Table I). Seven polymorphisms were reported in these studies: *FSHR* 919 G>A (rs 6165), *FSHR* 2039 G>A (rs6166), *FSHR* −29 G>A (rs1394205), *LHB* 82 T>C (rs1800447), *LHB* 1502 G>A (rs1056917), *LHCGR* 935 A>G (rs2293275) and *LHCGR* 3442–25 260 A>G (rs13405728).

Risk of bias within studies

Bias assessment within studies is shown in Table I. A high rate of agreement, evaluated by *k*-Cohen calculation, was observed between the two authors (A.C. and D.S.; *k*-Cohen = 0.83).

Summary of results

The results of the quantitative analysis of each outcome measure according to genotype distribution are reported below and summarized in Table II.

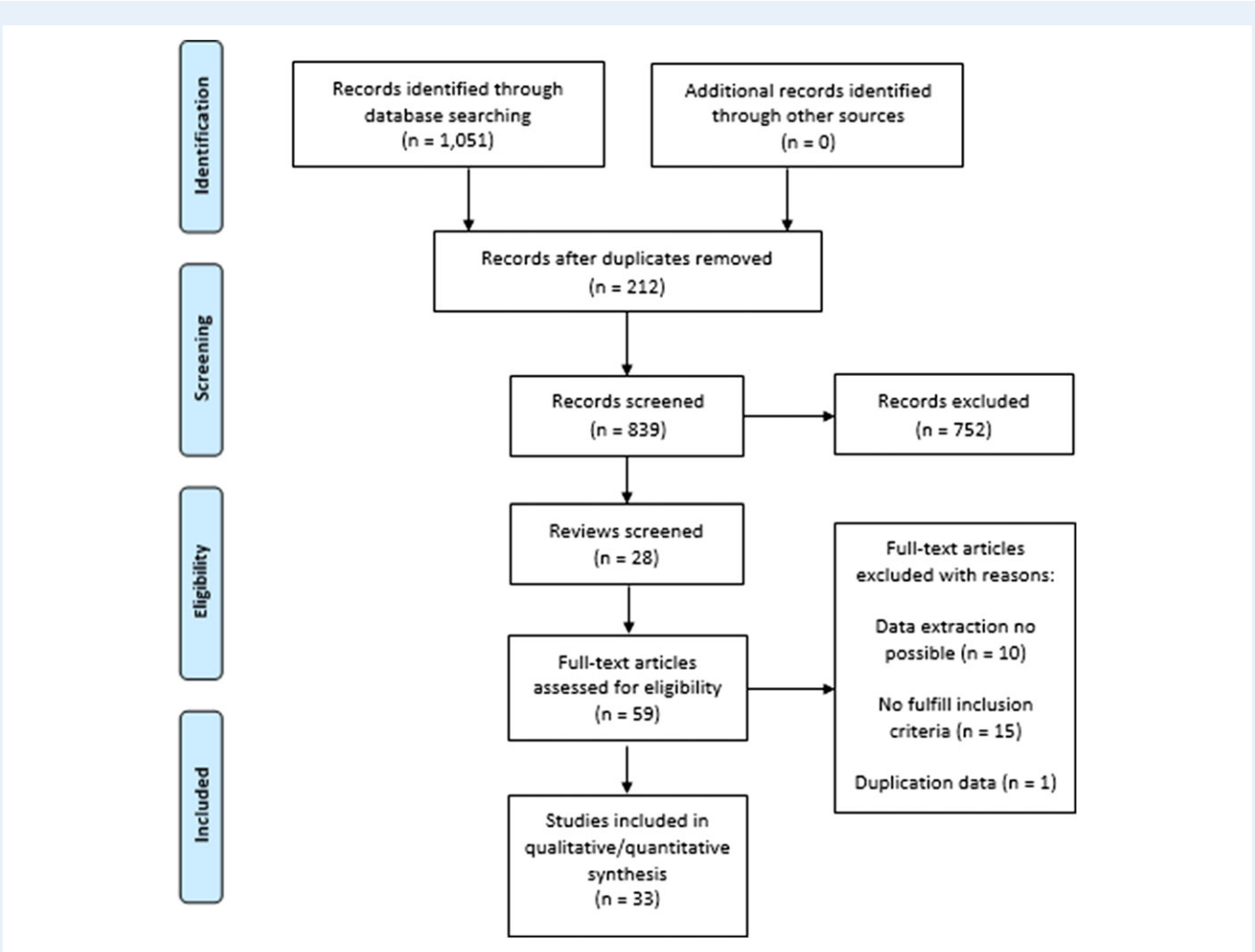

Figure 1 Study flow chart.

FSH consumption

A meta-analytic approach was possible only for *FSHR* (rs6165), *FSHR* (rs6166) *and FSHR* (rs1394205). No data were found regarding *LHB* (rs1056917).

Four studies (Laven *et al.*, 2003; Achrekar *et al.*, 2009a; Genro *et al.*, 2012; Yan *et al.*, 2013), for a total of 729 women, evaluated FSH consumption in relation to the *FSHR* (rs6165) genotype distribution. FSH consumption did not differ statistically among *FSHR* (rs6165) AA homozygotes, GG homozygotes (Random WMD: 227.64 IU, 95% CI: −452.95 to 908.22 IU, I^2 = 96%), and AG heterozygotes (Random WMD: 110.24 IU, 95% CI: −323.57 to 544.05 IU, I^2 = 93%). Similarly, FSH consumption did not differ between GG homozygotes and AG heterozygotes (Random WMD: 134.09 IU, 95% CI: −162.06 to 430.25, I^2 = 81%) (Supplementary Fig. S1).

Eighteen studies (Perez Mayorga *et al.*, 2000; Sudo *et al.*, 2002; Laven *et al.*, 2003; Behre *et al.*, 2005; Jun *et al.*, 2006; Loutradis *et al.*, 2006; Achrekar *et al.*, 2009a; Huang *et al.*, 2010, 2015; Nordhoff *et al.*, 2011; Sheikhha *et al.*, 2011; Anagnostou *et al.*, 2012; Genro *et al.*, 2012; Lledo *et al.*, 2013; Yan *et al.*, 2013; Mohiyiddeen *et al.*, 2013b; Lindgren *et al.*, 2016; Lledó *et al.*, 2016), for a total of 4 094 women, evaluated FSH consumption according to *FSHR* (rs6166) genotype distribution. FSH consumption in *FSHR* AA homozygotes was comparable to that in GG homozygotes (Random WMD: −158.50 IU, 95% CI: −338.32 to 21.32 IU, I^2 = 96%) and AG heterozygotes (Random WMD: 18.00 IU, 95% CI: −119.36 to 155.35 IU, I^2 = 96%). Similarly, no differences were found between *FSHR* GG homozygotes and AG heterozygotes (Random WMD: −137.53 IU, 95% CI: −293.04 to 17.97 IU, I^2 = 86%) (Supplementary Fig. S2).

Three studies (Achrekar *et al.*, 2009b; Desai *et al.*, 2011; Tohlob *et al.*, 2016), for a total of 709 women, evaluated FSH consumption according to the *FSHR* (rs1394205) genotype. The consumption of FSH was significantly lower in *FSHR* GG homozygotes than in *FSHR* AA homozygotes (Random WMD: −1294.61 IU, 95% CI: −1996.14 to −593.08, $P < 0.001$, Bonferroni adjusted $P = 0.008$, I^2 = 99%), whereas no differences were observed between GG and AG heterozygotes (Random WMD: −277.84 IU, 95% CI: −1145.28 IU to 589.60, I^2 = 100%). FSH consumption was lower in AG heterozygotes than in FSHR AA homozygotes (Random WMD: −1014.36 IU, 95% CI: −1664.61 to −364.11, $P = 0.002$, Bonferroni adjusted $P = 0.006$, I^2 = 99%) (Fig. 2).

Two studies (Alviggi *et al.*, 2011; Alviggi *et al.*, 2013) reported FSH consumption according to *LHB* (rs1800447) genotype distribution. Both reported a significantly higher FSH consumption in variant carriers compared with wild-type carriers.

Table I Characteristics and Newcastle–Ottawa scale score of studies included in a systematic review and meta-analysis of the impact of genetic variants of gonadotrophins and their receptors in controlled ovarian stimulation.

References	SNPs evaluated	Country	Number of patients	Mean age ± SD (years)	Study design	NOS score
Achrekar *et al.* (2009a)	*FSHR* (rs6165), *FSHR* (rs6166)	India	50	30.09 ± 1.50	Retrospective	7
Achrekar *et al.* (2009b)	*FSHR* (rs1394205)	India	150	NA	Retrospective	7
Alviggi *et al.* (2009)	*LHB* (rs1800447)	Italy	60	30.81 ± 3.39	Retrospective	6
Alviggi *et al.* (2013)	*LHB* (rs1800447)	Denmark	220	30.65 ± 3.95	Retrospective	6
Alviggi *et al.*, 2016a	*FSHR* (rs6166)	Italy	42	30.57 ± 4.37	Retrospective	6
Anagnostou *et al.* (2012)	*FSHR* (rs6166)	Greece	109	35.00 ± 4.50	Prospective	6
Behre *et al.* (2005)	*FSHR* (rs6166)	Germany	93	33.10 ± 0.64	Prospective	7
Dan *et al.* (2015)	*FSHR* (rs1394205)	China	158	NA	Prospective	7
Davar *et al.* (2014)	*LHB* (rs1056917)	Iran	220	29.94 ± 5.98	Prospective	7
De Castro *et al.* (2003)	*FSHR* (rs6166)	Spain	102	33.70 ± 3.10	Retrospective	6
Desai *et al.* (2011)	*FSHR* (rs1394205)	India	100	33.11 ± 0.82	Retrospective	8
Genro *et al.* (2012)	*FSHR* (rs6165), *FSHR* (rs6166)	Brazil	124	34.95 ± 3.82	Prospective	8
Huang *et al.* (2015)	*FSHR* (rs6166)	China	1250	31.31 ± 3.34	Retrospective	6
Huang *et al.* (2010)	*FSHR* (rs6166)	China	136	30.33 ± 3.31	Prospective	6
Jun *et al.* (2006)	*FSHR* (rs6166)	South Corea	263	32.60 ± 0.40	Prospective	7
Klinkert *et al.* (2006)	*FSHR* (rs6166)	The Netherlands	105	36.90 ± 5.10	Prospective	6
Laven *et al.* (2003)	*FSHR* (rs6165), *FSHR* (rs6166)	Holland	148	28.20 ± 3.10	Prospective	6
Lazaros *et al.* (2013)	*FSHR* (rs6165), *FSHR* (rs6166)	Greece	604	NA	Retrospective	6
Lindgren *et al.* (2016)	*LHCGR* (rs2293275), FSHR (rs6166)	Denmark	384	31.92 ± 2.90	Prospective	8
Lledo *et al.* (2013)	*FSHR* (rs6166)	Spain	145	25.60 ± 3.80	Retrospective	6
Lledo *et al.* (2016)	*FSHR* (rs6166)	Spain	191	25.60 ± 3.90	Retrospective	6
Loutradis *et al.* (2006)	*FSHR* (rs6166)	Greece	125	30.30 ± 3.00	Retrospective	5
Mohiyiddeen *et al.* (2013a)	*FSHR* (rs6166)	UK	212	33.17 ± 3.50	Prospective	7
Mohiyiddeen *et al.* (2013b)	*FSHR* (rs6166)	UK	504	33.50 ± 3.70	Prospective	7
Nordhoff *et al.* (2011)	*FSHR* (rs6166)	Germany	22	32.40 ± 3.35	Retrospective	3
Perez Mayorga *et al.* (2000)	*FSHR* (rs6166)	Germany	161	32.60 ± 0.50	Prospective	6
Yin *et al.* (2015)	*LHCGR* (rs13405728)	China	236	NA	Prospective	6
Sheikhha *et al.* (2011)	*FSHR* (rs6166)	Iran	108	29.63 ± 4.70	Retrospective	6
Sudo *et al.* (2002)	*FSHR* (rs6166)	Japan	522	31.83 ± 0.77	Retrospective	5
Tohlob *et al.* (2016)	*FSHR* (rs1394205)	UK	559	33.23 ± 5.1	Retrospective	6
Trevisan *et al.* (2014)	*FSHR* (rs6165), *FSHR* (rs6166)	Italy	149	NA	Retrospective	5
Yan *et al.* (2013)	*FSHR* (rs6165), *FSHR* (rs6166)	China	450	32.15 ± 4.96	Retrospective	6
Zalewski *et al.* (2013)	*FSHR* (rs6166)	Poland	22	33.10 ± 5.00	Retrospective	3

NOS, Newcastle–Ottawa scale; FSHR, FSH receptor; LHCGR, LHCG receptor; SNP, single nucleotide polymorphism; SD, standard deviation; NA, not available.

One study (Lindgren *et al.*, 2016) reported FSH consumption in relation to the distribution of the *LHCGR* (rs2293275) genotype. No significant differences among genotypes were detected.

One study (Yin *et al.*, 2015) reported FSH consumption in relation to the distribution of the *LHCGR* (rs13405728) genotype. No significant differences among genotypes were reported.

The overall effect estimated by the analyses indicated that FSH consumption was only affected by the presence of *FSHR* (rs1394205). However, these results may be conservative given the high heterogeneity among trials and the relatively small number of patients evaluated.

Stimulation duration

A meta-analytic approach regarding stimulation duration was possible only for *FSHR* (rs6165) and *FSHR* (rs6166). No data on the other polymorphisms were found.

Three studies (Laven *et al.*, 2003; Genro *et al.*, 2012; Yan *et al.*, 2013) for a total of 679 patients, evaluated stimulation duration in relation to the distribution of the *FSHR* (rs6165) genotype. The duration of stimulation did not differ between *FSHR* AA homozygotes and GG homozygotes (Random WMD: −0.59, 95% CI: −1.24 to 0.05, I^2 = 60%), however it was significantly shorter in AA than in AG heterozygotes (Fixed WMD: −0.48, 95% CI: −0.87 to −0.10,

Table II Pooled effect estimates including only FSH receptor haplotypes with significant overall effect on ovarian stimulation outcomes.

FSHR variant	Comparison	Parameter	Effect size [95% CI]	I^2%	Test for overall effect (*P*-value)
FSHR (rs6165)	AA versus GG	Stimulation duration	−0.59 [−1.24, 0.05]	60	NS
		Number of oocytes	1.85 [0.85, 2.85]	0	0.008*
	AA versus AG	Stimulation duration	−0.48 [−0.87, −0.10]	44	0.04*
		Number of oocytes	1.62 [0.28, 2.95]	56	0.052*
	AG versus GG	Stimulation duration	−0.29 [−0.95, 0.37]	0	NS
		Number of oocytes	−0.37 [−1.51, 0.78]	18	NS
FSHR (rs6166)	AA versus GG	Number of oocytes	0.84 [0.19, 1.49]	76	0.03*
		Number of MII oocytes	1.03 [0.01, 2.05]	0	NS
	AA versus AG	Number of oocytes	0.18 [−0.84, 0.48]	85	NS
		Number of MII oocytes	0.79 [−0.05, 1.62]	0	NS
	AG versus GG	Number of oocytes	0.88 [0.12, 1.63]	76	0.04*
		Number of MII oocytes	0.34 [−0.57, 1.26]	49	NS
FSHR (rs1394205)	GG versus AA	FSH consumption	−1294.61 [−1996.14,−593.08]	99	0.008*
	AA versus AG	FSH consumption	−1014.36 [−1664.61,−364.11]	99	0.006*
	AG versus GG	FSH consumption	−277.84 [−1145.28, 589.60]	100	NS

NS, not significant; *Bonferroni adjusted *P*-value.

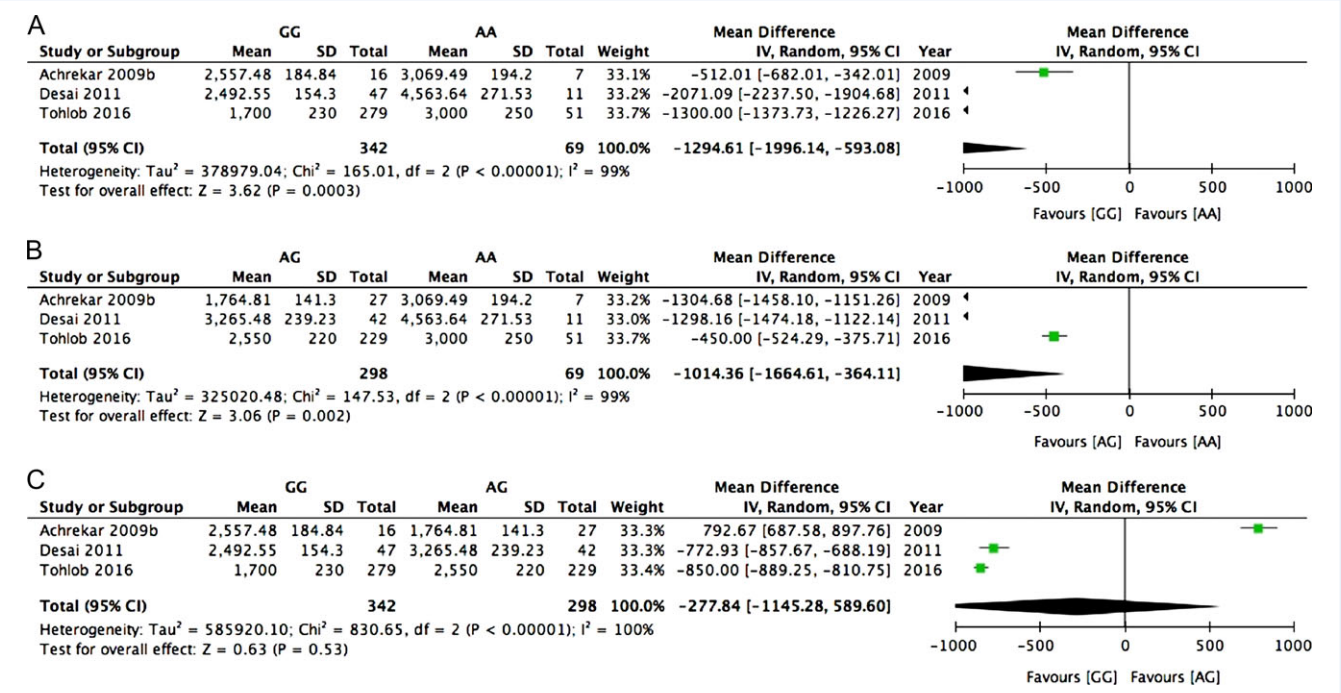

Figure 2 Forest plots of differences among *FSHR* (rs1394205) genotype carriers in relation to FSH consumption. (**A**) (rs1394205) G homozygotes versus A homozygotes. (**B**) (rs1394205) heterozygotes versus A homozygotes. (**C**) (rs1394205) G homozygous versus heterozygous.

P = 0.01, Bonferroni adjusted *P* = 0.04, I^2 = 44%). On the contrary, stimulation duration did not differ between *FSHR* GG homozygotes and AG heterozygotes (Fixed WMD −0.29, 95% CI: −0.95 to 0.37, I^2 = 0%) (Fig. 3).

Fifteen studies (De Castro *et al.*, 2003; Laven *et al.*, 2003; Behre *et al.*, 2005; Klinkert *et al.*, 2006; Loutradis *et al.*, 2006; Huang *et al.*, 2010; Nordhoff *et al.*, 2011; Genro *et al.*, 2012; Lledo *et al.*, 2013; Yan *et al.*, 2013; Zalewski *et al.*, 2013; Huang *et al.*, 2015; Alviggi *et al.*, 2016a) for a total of 3 069 women, evaluated stimulation duration in relation to the distribution of the *FSHR* (rs6166) genotype. The duration of stimulation did not differ among *FSHR* AA homozygotes, GG homozygotes (Fixed WMD: −0.01, 95% CI: −0.16 to 0.14 days, I^2 = 17%) and AG heterozygotes (Fixed WMD: 0.01, 95% CI: −0.04 to 0.05, I^2 = 27%). Lastly, no differences were observed between *FSHR* GG homozygotes and *FSHR* AG heterozygotes (Fixed WMD: −0.12, 95% CI: −0.29 to 0.04, I^2 = 2%) (Supplementary Fig. S3).

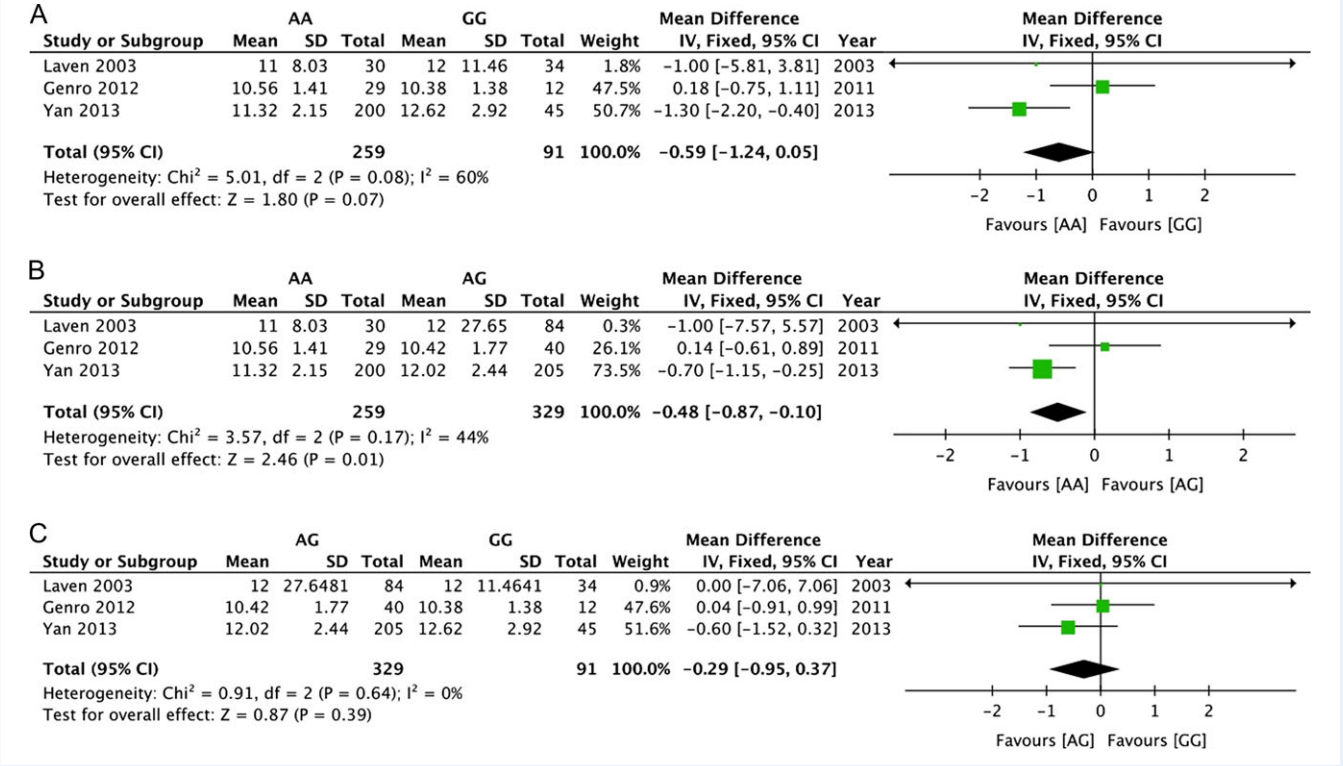

Figure 3 Forest plots of differences among *FSHR* (rs6165) genotype carriers in relation to stimulation duration. (**A**) (rs6165) A homozygotes versus G homozygotes. (**B**) (rs6165) A homozygotes versus heterozygotes. (**C**) (rs6165) heterozygous versus G homozygotes.

In summary, the only difference observed was a shorter duration of stimulation in *FSHR* (rs6165) AA homozygotes than in AG heterozygotes.

Number of oocytes retrieved

A meta-analytic approach was possible only for *FSHR* (rs6165), *FSHR* (rs6166) and *FSHR* (rs1394205). No data were found regarding *LHCGR* (rs2293275).

Five studies (Achrekar *et al.*, 2009a; Genro *et al.*, 2012; Lazaros *et al.*, 2013; Yan *et al.*, 2013; Trevisan *et al.*, 2014), for a total of 1020 women, reported the number of oocytes retrieved in relation to the distribution of the *FSHR* (rs6165) genotype. The number of oocytes retrieved was significantly higher in AA homozygotes than in either GG homozygotes (Fixed WMD: 1.85, 95% CI: 0.85–2.85, $P < 0.001$, Bonferroni adjusted $P = 0.008$, $I^2 = 0\%$). No difference was detected among AG heterozygotes, GG homozygotes (Fixed WMD: −0.37, 95% CI: −1.51 to 0.78, $I^2 = 18\%$) and AA homozygotes (Random WMD: 1.62, 95% CI: 0.28–2.95, $P = 0.02$, Bonferroni adjusted $P = 0.052$, $I^2 = 56\%$) (Fig. 4). The additive model was marginally significant in the association between *FSHR* (rs6165) and number of oocytes retrieved (pooled Hedges' g −0.129; Fixed: 95% CI −0.258 to 0.000, $P = 0.05$, $I^2 = 43\%$).

Twenty-one studies (Perez Mayorga *et al.*, 2000; Sudo *et al.*, 2002; De Castro *et al.*, 2003; Behre *et al.*, 2005; Jun *et al.*, 2006; Klinkert *et al.*, 2006; Loutradis *et al.*, 2006; Achrekar *et al.*, 2009a; Huang *et al.*, 2010, 2015; Nordhoff *et al.*, 2011; Sheikhha *et al.*, 2011; Genro *et al.*, 2012; Lazaros *et al.*, 2013; Lledo *et al.*, 2013, 2016; Yan *et al.*, 2013; Zalewski *et al.*, 2013; Mohiyiddeen *et al.*, 2013b; Trevisan *et al.*, 2014; Alviggi *et al.*, 2016a) including 4 425 women, reported the number of oocytes retrieved in relation to the distribution of the *FSHR* (rs6166) genotype. The number of oocytes retrieved was significantly higher in AA homozygotes than in GG homozygotes (Random WMD: 0.84, 95% CI: 0.19–1.49, $P = 0.01$, Bonferroni adjusted $P = 0.03$, $I^2 = 76\%$), but it was similar to that retrieved from AG heterozygotes (Random WMD: −0.18, 95% CI: −0.84 to 0.48, $I^2 = 85\%$). The number of oocytes was significantly higher in AG heterozygotes than in GG homozygotes (Random WMD: 0.88, 95% CI: 0.12–1.63, $P = 0.02$, Bonferroni adjusted $P = 0.04$, $I^2 = 76\%$) (Fig. 5). The additive model was not significant for the association between *FSHR* (rs6165) and number of oocytes retrieved (pooled Hedges' g −0.072 95% CI −0.179 to 0.035, $P = 0.19$, $I^2 = 65\%$).

Three studies (Achrekar *et al.*, 2009b; Desai *et al.*, 2011; Tohlob *et al.*, 2016), including 709 women, evaluated the number of oocytes retrieved in relation to the distribution of the *FSHR* (rs1394205) genotype. The number of oocytes retrieved was lower, albeit not significantly lower, in *FSHR* (rs1394205) AA homozygotes than in either GG homozygotes (Random WMD: −5.20, 95% CI: −11.22 to 0.82, $I^2 = 99\%$) or AG heterozygotes (Random WMD: −3.88, 95% CI: −7.93 to 0.18, $I^2 = 98\%$). No differences were observed between GG homozygotes and AG heterozygotes (Random WMD: −1.29, 95% CI: −3.51 to 0.93, $I^2 = 97\%$) (Supplementary Fig. S4).

Two studies (Alviggi *et al.*, 2011; Alviggi *et al.*, 2013) reported the number of oocytes retrieved in relation to the distribution of the *LHB* (rs1800447) genotype. In both studies, the number of oocytes retrieved did not differ among genotypes.

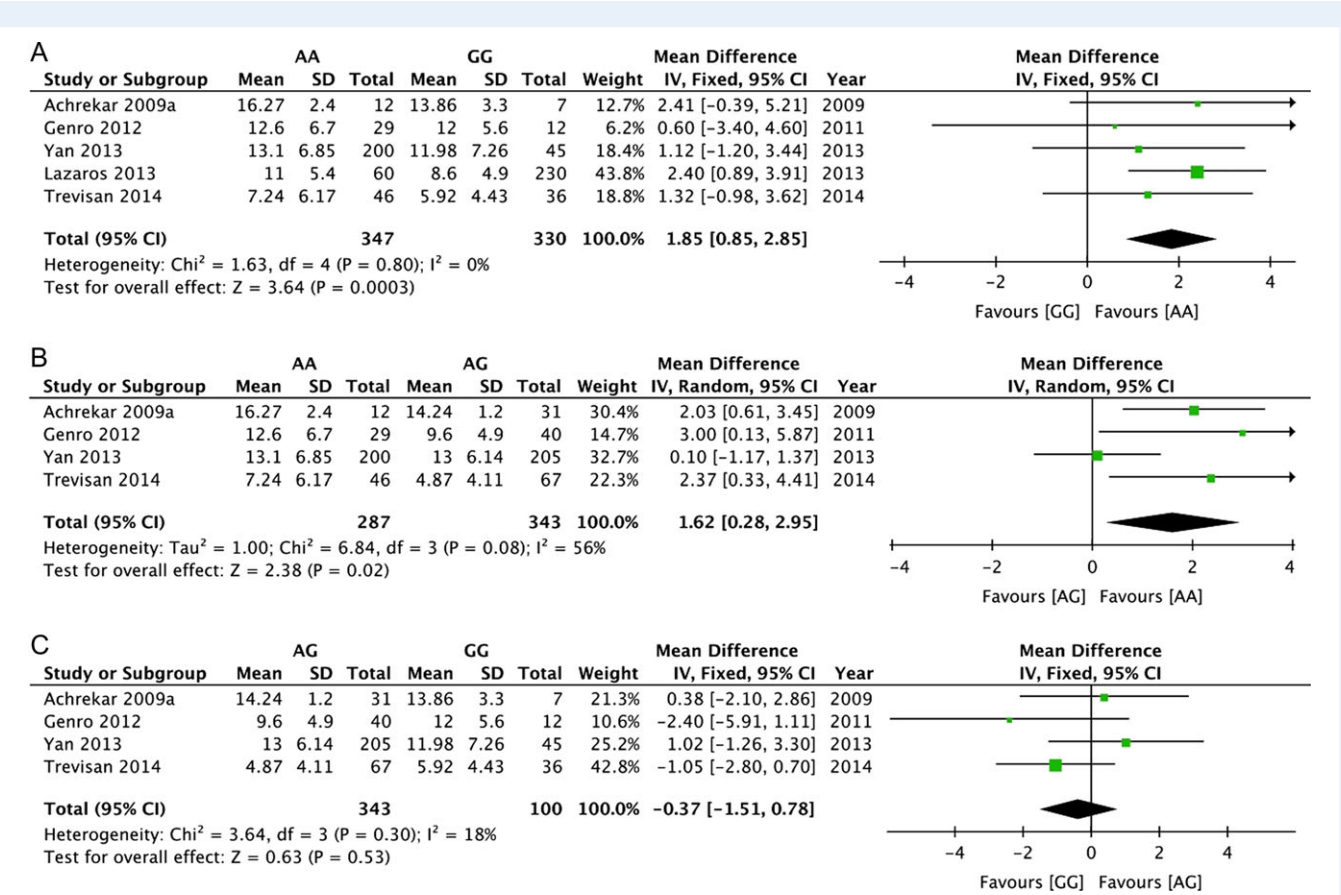

Figure 4 Forest plots of differences among *FSHR* (rs6165) genotype carriers in relation to the number of oocytes retrieved. (**A**) (rs6165) A homozygotes versus G homozygotes. (**B**) (rs6165) A homozygotes versus heterozygotes. (**C**) (rs6165) heterozygous versus G homozygotes.

Only one study (Davar *et al.*, 2014) reported the number of oocytes retrieved in relation to the *LHB* (rs1056917) genotype, and no significant differences among genotypes were observed.

Similarly, only one study (Yin *et al.*, 2015) reported the number of oocytes retrieved in relation to the distribution of the *LHCGR* (rs13405728) genotype, and there were no significant differences among genotypes.

The overall effect size indicates that the *FSHR* (rs6165) and *FSHR* (rs6166) genotypes impacted on the number of oocytes retrieved. In both cases, AA homozygosity was associated with a higher number of oocytes retrieved, whereas GG homozygotes exerted an opposite effect. The effect size estimated for the *FSHR* (rs6166) genotype may be conservative because of the high heterogeneity.

Number of MII oocytes

A meta-analytic approach was possible only in the case of *FSHR* (rs6166). No data were found regarding *LHB* (rs1056917).

Only two studies (Genro *et al.*, 2012; Trevisan *et al.*, 2014) evaluated the number of MII oocytes retrieved in relation to *FSHR* (rs6165). In both studies, the number of MII oocytes did not differ among genotypes.

Five studies (Genro *et al.*, 2012; Mohiyiddeen *et al.*, 2013a; Trevisan *et al.*, 2014; Lindgren *et al.*, 2016; Lledó *et al.*, 2016) including 1185 patients, reported the number of MII oocytes retrieved in relation to the distribution of the *FSHR* (rs6166) genotype. The number of MII oocytes was higher in AA homozygotes than in GG homozygotes but the differences did not reach statistical significance after Bonferroni correction (Fixed WMD: 1.03, 95% CI: 0.01–2.05, $P = 0.05$, Bonferroni adjusted $P = 0.14$, $I^2 = 0\%$). No significant differences were observed between AA homozygotes and AG heterozygotes (Fixed WMD: 0.79, 95% CI: −0.05 to 1.62, $I^2 = 0\%$), or between GG homozygotes and AG heterozygotes (Fixed WMD: 0.34, 95% CI: −0.57 to 1.26, $I^2 = 49\%$) (Supplementary Fig. S5).

Only two studies (Desai *et al.*, 2011; Dan *et al.*, 2015) reported the number of MII oocytes in relation to the distribution of the *FSHR* (rs1394205) genotype. In detail, Dan *et al.* (2015) observed a significantly higher number of MII oocytes in GG carriers than in AG/AA carriers. Similarly, Desai *et al.* (2011) found a significantly higher number of MII oocytes in GG carriers than in AG and AA carriers.

The only study to report the number of MII oocytes retrieved in relation to the *LHB* (rs1800447) genotype did not find any difference between wild-type and variant carriers (Alviggi *et al.*, 2013). Similarly, the only study to report the number of MII oocytes retrieved in

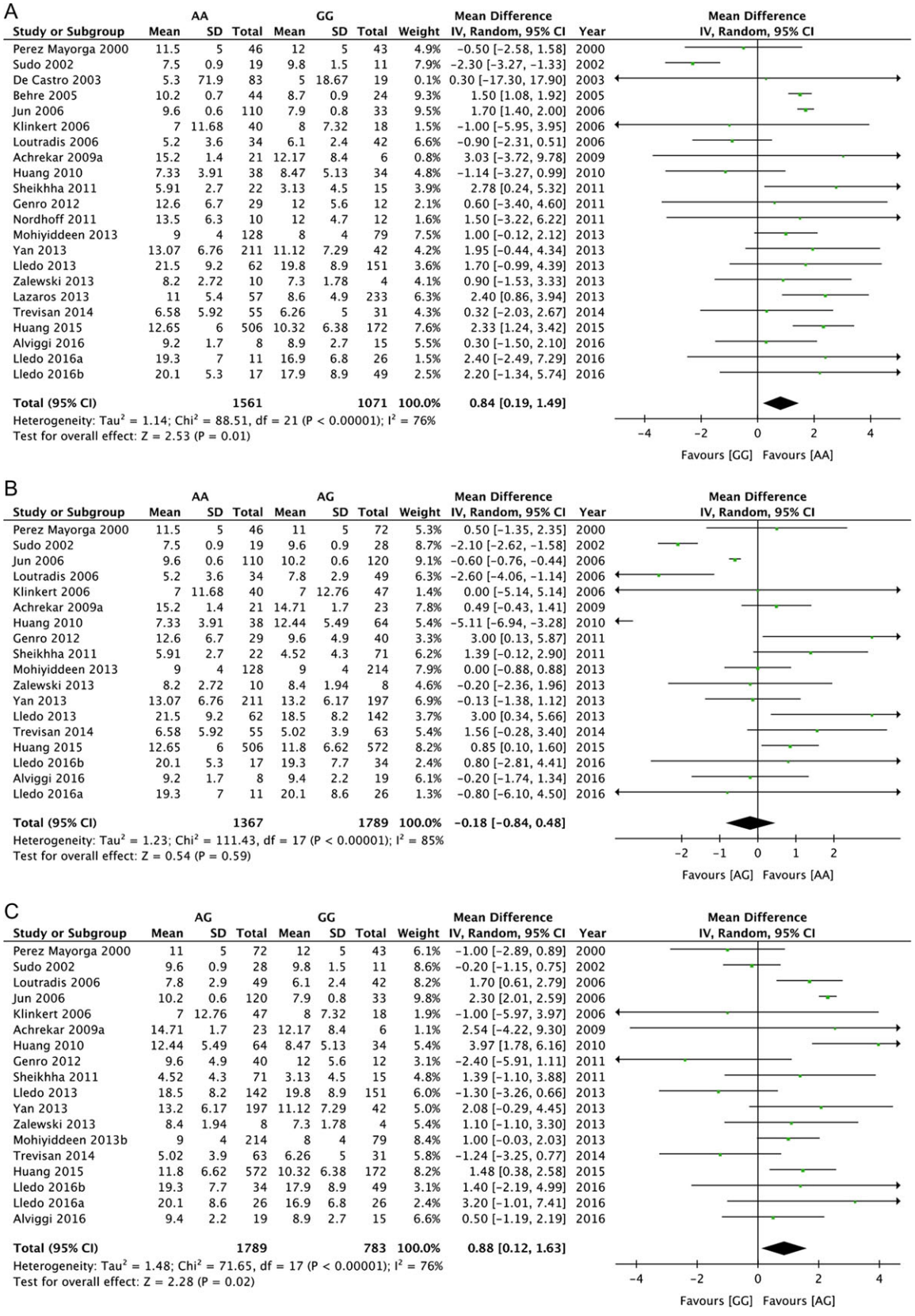

Figure 5 Forest plots of differences among *FSHR* (rs6166) genotype carriers in relation to the number of oocytes retrieved. (**A**) (rs6166) A homozygotes versus G homozygotes. (**B**) (rs6166) A homozygotes versus heterozygotes. (**C**) (rs6166) heterozygotes versus G homozygotes.

relation to the *LHCGR* (rs2293275) genotype did not find any difference among the haplotypes identified (Lindgren *et al.*, 2016). The only study to report the number of MII oocytes retrieved in relation to the distribution of the *LHCGR* (rs13405728) genotype did not find any differences among genotypes (Yin *et al.*, 2015).

The overall effect size indicates that the *FSHR* (rs6166) genotype did not significantly affect the number of mature oocytes retrieved. However, given the limited number of studies available, these observations should be viewed with caution.

OPR

A meta-analytic approach to OPR was possible only for *FSHR* (rs6166). No data were found regarding the *FSHR* (rs6165), *LHB* (rs1056917) or *LHCGR* (rs13405728) genotypes.

Seven studies (Jun *et al.*, 2006; Sheikhha *et al.*, 2011; Lledo *et al.*, 2013; Mohiyiddeen *et al.*, 2013b; Huang *et al.*, 2015; Lindgren *et al.*, 2016; Alviggi *et al.*, 2016a) including 3191 patients, evaluated OPR in relation to the distribution of the *FSHR* (rs6166) genotype. The overall OR did not differ among AA homozygotes, GG homozygotes (Fixed OR: 0.89, 95% CI: 0.70–1.12, I^2 = 0%) and AG heterozygotes (Fixed OR: 0.97, 95% CI: 0.82–1.16, I^2 = 29%). Moreover, no significant differences were observed between GG homozygotes and AG heterozygotes (Fixed OR: 0.95, 95% CI: 0.77–1.18, I^2 = 0%) (Supplementary Fig. S6).

Only two studies (Achrekar *et al.*, 2009b; Tohlob *et al.*, 2016) reported OPR in relation to *FSHR* (rs1394205). Achrekar *et al.* (2009b) reported a comparable OPR among GG, AG and AA carriers, whereas Tohlob *et al.* (2016) reported a higher OPR in women carrying the A allele than in those carrying the G allele (crude OR 1.32, 95% CI 1.01–1.74, P = 0.04), but this association was not significant when adjusted for the number of embryos transferred.

The only study to report OPR in relation to *LHB* (rs1800447) did not find any difference between wild-type and variant carriers (Alviggi *et al.*, 2013).

Only one study (Lindgren *et al.*, 2016) reported OPR in relation to *LHCGR* (rs2293275). Differences in terms of OPR were observed among haplotypes (AA: 18%; AG: 27%; GG: 31%, P = 0.037), with a higher prevalence in GG carriers.

Risk of bias across studies

The risk of significant bias across studies regarding the primary outcome was rejected by Egger's test (P = 0.828 for *FSHR* rs6166; P = 0.27 for *FSHR* rs6165, and P = 0.12 for *FSHR* rs1394205), visual inspection of the funnel plots, and the trim and fill method (Supplementary Fig. S7).

Subgroup and sensitivity analyses

We estimated the number of oocytes retrieved according to type of gonadotrophin, namely recombinant versus urinary FSH (Fig. 6). We did not include papers in which both gonadotrophins were used for COS (Behre *et al.*, 2005; Jun *et al.*, 2006; Huang *et al.*, 2010; Sheikhha *et al.*, 2011; Mohiyiddeen *et al.*, 2013b) or in which the formulation adopted was not clearly stated (Achrekar *et al.*, 2009a). While a higher number of oocytes were retrieved in AA *FSHR* (rs6166) carriers than in GG carriers when recombinant FSH was used (Fixed WMD 1.15, 95% CI 0.53-1.76, P = 0.0003, Bonferroni

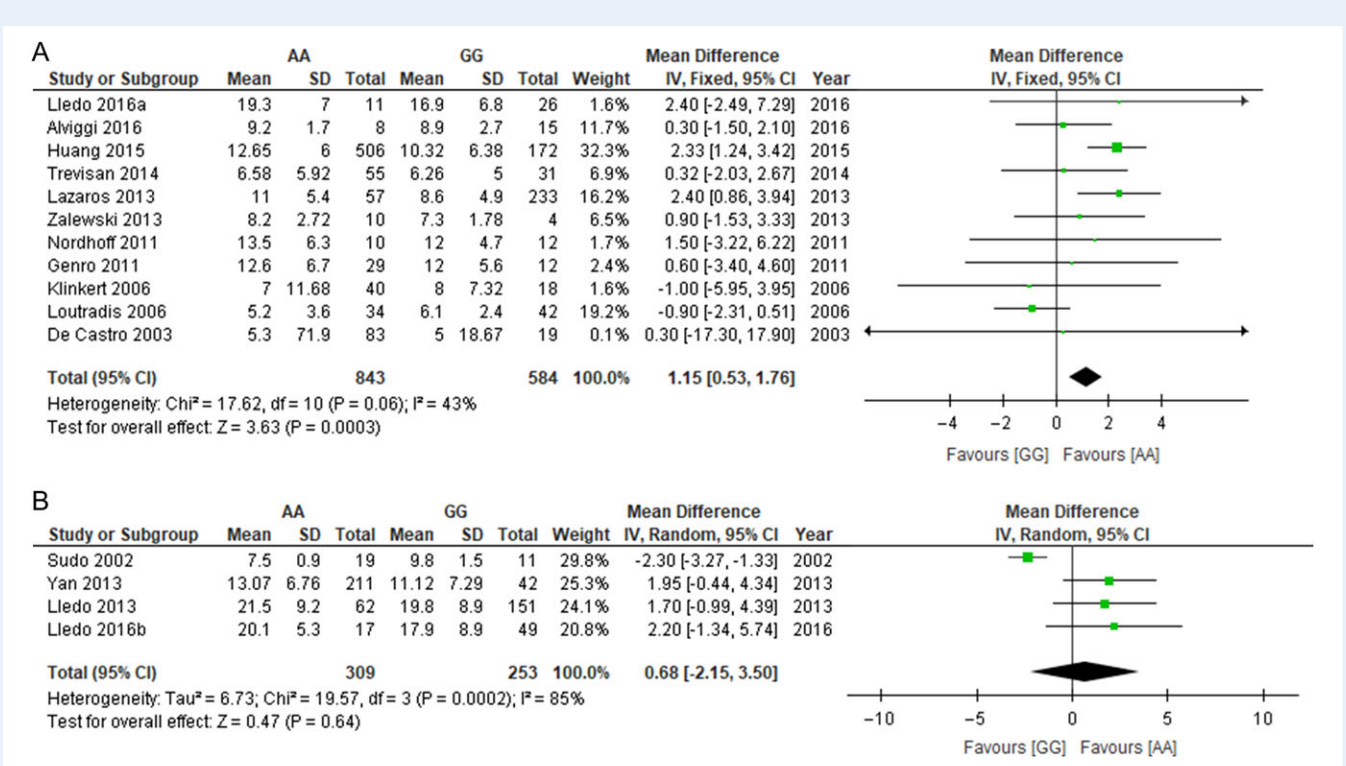

Figure 6 Forest plots of differences between *FSHR* (rs6166) AA versus GG carriers considering the number of oocytes retrieved oocytes retrieved. (**A**) recombinant gonadotropin (**B**) urinary gonadotropin.

adjusted 0.0009, I^2 = 43%) no differences were observed when urinary gonadotrophin was used (Random WMD 0.68, 95% CI: −2.19 to 3.54; I^2 = 86%). Concerning the *FSHR* (rs6165) genotype, FSH basal levels did not differ among haplotypes after Bonferroni correction (Supplementary Fig. S8). On the other hand, FSH basal levels were significantly lower in AA than in GG FSHR (rs6166) carriers (Fixed WMD −0.54, 95% CI −0.72 −0.36, $P < 0.00001$, Bonferroni adjusted $P < 0.0001$, I^2 = 21%) (Fig. 7).

Lastly, sensitivity analysis revealed that the pooled effect sizes were affected only with regard to the number of retrieved oocytes between FSHR (rs6165) AA and AG carriers (Supplementary Table II).

Discussion

Summary of evidence

We conducted this systematic review in the attempt to unravel the role of gene polymorphisms of gonadotrophins and their receptors on the outcome of COS. We evaluated OPR rather than live birth rate because the many features that can affect the later stages of pregnancy may confound the impact of folliculogenesis-related polymorphisms. Our findings indicate that FSHR polymorphisms affect the outcome of COS. In particular, FSH consumption was higher in A allele homozygous carriers of the *FSHR* (rs1394205) genotype. Furthermore, the number of oocytes retrieved was significantly higher in *FSHR* (rs6165) AA carriers, and ovarian stimulation was significantly shorter in these patients than in GG and AG carriers. Similarly, the number of oocytes retrieved was significantly higher in *FSHR* (rs6166) AA carriers than in GG carriers. Although neither polymorphism had an additive effect, a significant impact on the number of oocytes was observed under co-dominance (AA versus GG and AG versus GG) for *FSHR* rs6166 and only under homozygote models (AA versus GG) for *FSHR* rs6165. Therefore, both *FSHR* polymorphisms seem to influence responsiveness to COS treatment.

Gonadotrophin type seems to affect the number of oocytes retrieved in relation to *FSHR* (rs6166) genotype distribution. In fact, the number of oocytes retrieved was significantly higher in AA carriers than in GG carriers when recombinant FSH was used but not when urinary FSH was used. *FSHR* (rs6166) also affects endogenous levels of FSH as shown by the finding of higher plasma FSH values in GG carriers than in AA carriers. Lastly, the *FSHR* (rs6166) genotype did not significantly affect OPR.

The results of our review of gonadotrophins and their receptor polymorphisms conducted with a quantitative approach are consistent with those reported in qualitative reviews (Altmae *et al.*, 2011). However, it remains to be determined whether a pharmacogenomic approach could counteract the effect of such polymorphisms. Behre *et al.* (2005) partially addressed this issue by stratifying normogonadotrophic patients according to the distribution of the *FSHR* (rs6166) genotype, and found that increasing daily FSH dose from 150 to 225 IU/day counteracted the lower estradiol levels in GG carriers.

Given the paucity of data, we were unable to carry out a meta-analysis of remnant gonadotrophins and their receptor polymorphisms [LHB (rs1800447), LHB 1502 G>A (rs1056917), LHCGR 935 A>G (rs2293275) and LHCGR 3442–25 260 A>G (rs13405728)].

In summary, our meta-analysis demonstrates that specific polymorphisms of gonadotrophins and their receptors modulate the ovarian response to exogenous FSH. On the other hand, further studies are required to evaluate the impact of these polymorphisms on OPR and live birth rate. In this context, it is noteworthy that ART births are greatly influenced by various factors, most of which occur during the late stages of pregnancy and transcend the 'physiological' effects of gonadotrophins and their receptors. In other words, we maintain that the ovarian response is more reliable than pregnancy rate in determining the effect of gonadotrophins and their receptor polymorphisms on COS.

Interpretation of results and clinical considerations

Our findings can be related to the molecular characteristics of the genotypes associated with the response to COS (Table III). The *FSHR* gene carries more than 2000 SNPs, although only *FSHR* (rs6165) and *FSHR* (rs6166) seem to play a prominent role in the response to COS. Both SNPs cause an amino acid exchange: in *FSHR* (rs6166), asparagine is substituted by serine thereby introducing a potential phosphorylation site, whereas in *FSHR* (rs6165) threonine is substituted by alanine, which results in a change from a polar to a nonpolar hydrophobic amino acid thereby removing a potential O-linked glycosylation site. These genotypes are in nearly complete linkage disequilibrium, except in some African populations (Simoni and Casarini, 2014; Casarini *et al.*, 2015). *In vitro* studies conducted using human granulosa cells showed that GG carriers of the *FSHR* (rs6166) genotype have greater resistance to FSH than do AA carriers (Casarini *et al.*, 2014, 2015). Our findings corroborate these previous observations. Indeed, we found that GG *FSHR* (rs6166) carriers had higher ovarian resistance to exogenous gonadotrophin and consequently had fewer oocytes compared with AA carriers. Moreover, we demonstrate that such FSHR resistance involves also endogenous FSH levels, as reported elsewhere (Fig. 7) (Mohiyiddeen and Nardo, 2010). These effects corroborate the potential impaired function of FSHR in G allele carriers and could explain why GG allele carriers have an impaired prognosis to COS as fewer oocytes are collected in these patients. FSHR function is controlled in both men and women by another FSH beta subunit (rs10835638) polymorphism (Grigorova *et al.*, 2010; Ferlin *et al.*, 2011; La Marca *et al.*, 2013), which is significantly correlated with FSH beta subunit transcriptional activity and metabolism (Hoogendoorn *et al.*, 2003). There is also evidence that *FSHR* (rs6166) could interact with polymorphisms that influence ART outcomes. Indeed, in a large cohort study, *FSHR* (rs6166) and *LHCGR* (rs2293275) allele G carriers had a 4-fold increased chance of pregnancy versus A carriers of both polymorphisms. Moreover, the number of mature oocytes was significantly higher in subjects with *FSHR* (rs1394205) GG plus *FSHR* (rs6166) AA genotypes than in other genotype combinations of these polymorphisms (Desai *et al.*, 2013).

The finding of Borgbo *et al.* (2015) that *FSHR* (rs6166) and *FSHR* (rs6165) GG carriers had higher *LHCGR* gene expression but lower anti-Müllerian hormone (AMH) receptor-2 expression versus carriers of other haplotypes suggested that these polymorphisms could affect the protein expression of human antral follicles. Nonetheless, it remains to be established whether *FSHR* (rs6166) and *FSHR* (rs6165) affect FSHR protein expression.

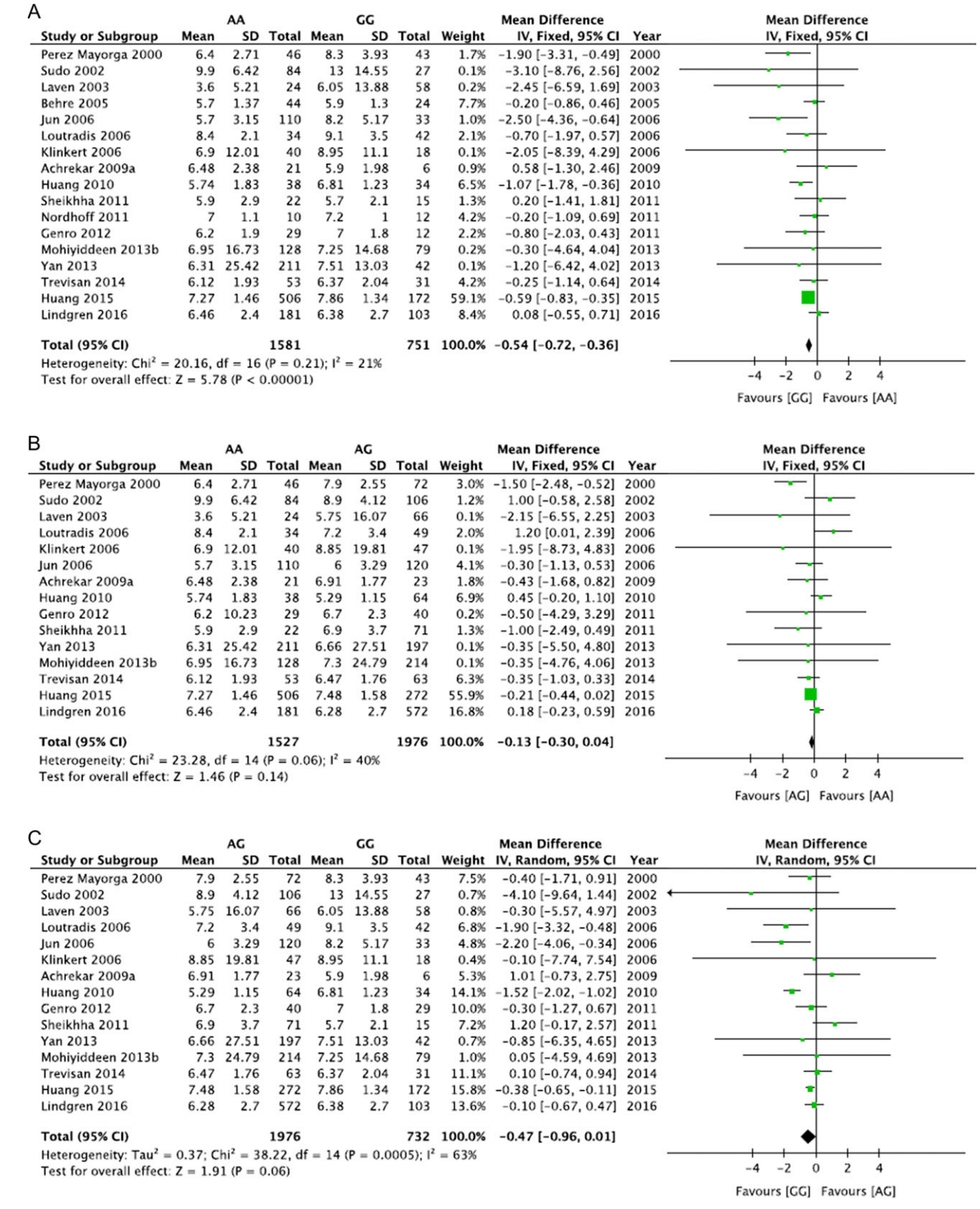

Figure 7 Forest plots of differences among *FSHR* (rs6166) genotype carriers considering FSH basal levels. (**A**) (rs6166) A homozygotes versus G homozygotes. (**B**) (rs6166) A homozygotes versus heterozygotes (**C**) (rs6166) heterozygotes versus G homozygotes.

Table III Worldwide distribution, pathogenic mechanism and clinical effects of SNPs significantly related to COS outcome.

Gene	refSNP	Chromosome	DNA nucleotide	Ancestral allele	Amino acid and allele	Worldwide distribution	Protein	Pathogenic mechanism	Clinical effect
FSHR	rs6166	2	c.919 G>A	G	A = Asn = N G = Ser = S	G allele is highly prevalent in North-Western Pakistan, Siberia, Mato Grosso, (Brazil) and Oceania (Simoni and Casarini, 2014)	N680S	Greater in vivo resistance to FSH activity Casarini *et al.* (2014)	Higher FSH basal levels in G carriers Perez Mayorga *et al.* (2000); Huang *et al.* (2015) Highest amount of FSH required during COS in G carriers
FSHR	rs6165	2	c.2039 G>A	A	A = Thr = T G = Ala = A	G allele shows a similar distribution of rs6166 with exception of African population (African ancestry in Southwest USA, Kenya, Nigeria) (Simoni and Casarini, 2014)	T307A	Greater in vivo resistance to FSH activity Simoni and Casarini (2014)	Higher FSH basal levels Yan *et al.* (2013) Highest amount of FSH required during COS in T carriers Achrekar *et al.* (2009a)
FSHR	rs1394205	2	c.–29 G>A	G	/	A allele highly prevalent in African population and Central South Asia population Simoni and Casarini (2014)	/	A allele showed reduced transcriptional activity compared with G allele (Nakayama *et al.*, 2006)	Higher amount of FSH required during COS In allele A carriers Achrekar *et al.* (2009b)
LHB	rs1800447	19	c.82 T>C	T	T = Trp = W C = Arg = R	C allele highly prevalent in Australian aboriginal and Finnish populations (Nilsson *et al.*, 1998)	W8R	Shorter half-life than wild-type form (Haavisto *et al.*, 1995)	Higher amount of exogenous FSH required during COS Alviggi *et al.* (2011); Alviggi *et al.* (2013)
LHCGR	rs2293275	2	c. 935 A>G	A	A = Asn = N G = Ser = S	G allele highly expressed in Asian and Ethiopian population (ALFRED database https://alfred.med.yale.edu/alfred/mvograph.asp?siteuid=SI323604S)	N312S	Impaired second messenger (cAMP) pathway Lindgren *et al.* (2016)	Higher ongoing pregnancy rate in SS carriers Lindgren *et al.* (2016)

COS, controlled ovarian stimulation.

Despite the linkage disequilibrium between *FSHR* (rs6165) and *FSHR* (rs6166), we decided to report the two polymorphisms separately for two reasons. Firstly, as stated above, the linkage disequilibrium between them is not universal (Simoni and Casarini, 2014). Secondly, they seem to be associated with different COS outcomes. For instance, Achrekar *et al.* (2009a) detected significant differences in terms of total FSH consumption among *FSHR* (rs6165) genotypes but not among *FSHR* (rs6166) genotypes. In addition, Trevisan *et al.* (2014) observed that only the *FSHR* (rs6165) genotype influences the number of embryos produced. Thus, these studies suggest that, although in linkage disequilibrium, these two polymorphisms could influence COS outcome in a different way.

The *FSHR* (rs1394205) polymorphism located in the 5′-untranslated region of the gene has been extensively studied in association with ovarian response. In Chinese hamster ovary cells, the transcription activity of *FSHR* was significantly lower in A allele carriers than in G allele carriers (Nakayama *et al.*, 2006). In another study, even the expression of *FSHR* was significantly lower in AA than in GG carriers (Desai *et al.*, 2011). Furthermore, the relative level of protein expression and membrane receptor expression in cumulus cells was significantly lower in AA carriers than in carriers of other haplotypes (Desai *et al.*, 2011). Consequently, basic science evidence suggests that the postulated role of *FSHR* (rs1394205) is more relevant in modulating FSHR protein function versus *FSHR* (rs6166) and *FSHR* (rs6165). At clinical level, we observed that *FSHR* (rs1394205) AA carriers have a higher FSH consumption in COS than carriers of the GG and AG haplotypes, and therefore, AA carriers may have an impaired response to ovarian stimulation.

Limitations and strengths

Like all meta-analyses, our study has several limitations. First, most of the studies included were observational and retrospective, and thus more prone to bias. Second, the number of studies evaluating COS outcomes in relation to the patient's gonadotrophin receptor genotype is relatively small. Third, it was not possible to evaluate the effect of alternate alleles on our findings because most trials did not evaluate more than one SNP simultaneously. Fourth, the studies included in our review were highly heterogeneous. This could be probably explained by the wide variation in terms of populations and treatment strategies. Lastly, OPRs were inconsistently reported in the included studies, however, we were able to conduct a meta-analysis for OPR with regard to the *FSHR* (rs6166), involving an elevated number of observations (over 3000 patients). We used several strategies to overcome these limitations. First, we applied random-effect model to strengthen the validity of our results in case of substantial heterogeneity among trials. Furthermore, we conducted a sensitivity analysis in which we considered only papers with a low risk of bias, namely those with a NOS score above 6. The observed pooled effect sizes did not differ significantly from the overall analysis except in a few cases. Hence, the consistency in the direction of our findings is reliable and the methods were applied rigorously.

Future research

The pharmacogenomic approach to medical care is becoming a reality in several fields, notably for patients at a high risk of adverse drug reactions (Sychev and Malova, 2015). In the ART setting, a pharmacogenomic approach to COS could lead to better standardization of treatment, thereby increasing the chance of ART success and reducing a potentially life-threatening excessive ovarian response.

Remarkably, no large randomized clinical trial on this topic has yet been conducted notwithstanding the relatively high number of studies published over the last 20 years. We believe that the pharmacogenomic approach to COS is still a largely neglected topic in the reproductive field. Furthermore, it noteworthy that most of the polymorphisms reported in our review are widespread in the general population and in women with reproductive disorders (Nilsson *et al.*, 1997; Alviggi *et al.*, 2009, 2015; Simoni and Casarini, 2014), and that genotype analysis can now be provided at the same costs of other commonly used analyses (e.g. AMH, antral follicle count).

Conclusion

Our systematic review indicates that specific SNPs of the gonadotrophins and their receptors influence COS outcomes. This evidence is supported by a large number of trials mainly devoted to *FSHR* (rs6165) and *FSHR* (rs6166) polymorphisms. Our analysis shows that a higher FSH consumption is expected in homozygotes for the A allele of the *FSHR* (rs1394205) polymorphism than carriers of the G allele. Moreover, FSHR (rs6166) GG homozygotes seem to be less responsive to COS treatment. In fact, they have fewer oocytes than do AA and AG carriers. It is feasible that the effect of these polymorphisms on COS may partially explain the phenomenon of 'hypo-response' that has been reported in 10–15% of normogonadotrophic ART women (Alviggi *et al.*, 2006; 2013). This peculiar ovarian response profile was recently included in the new classification of low prognosis women (Humaidan *et al.*, 2016; Poseidon *et al.*, 2016). Given the overall effect of gonadotrophins and their receptor SNPs on COS, a pharmacogenomic approach seems a promising strategy with which to improve the clinical management of infertile women candidates for COS.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

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Authors' roles

C.A., A.C., D.S., S.E., C.Y.A., P.H., G.D. and M.S. participated in study design. C.A., A.C., D.S. and S.E. wrote the first draft of the manuscript; A.C., D.S. and P.C. performed the statistical analysis; all authors contributed to critical discussion and to final version of the paper.

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Conflict of interest

Prof. C.A. reports personal fees honoraria from Merck outside the submitted work. Prof. P.H. reports unrestricted research grants from MSD, Merck and Ferring as well as personal fees from honoraria for lectures from MSD, Merck and Finox, outside the submitted work. Prof. S.C.E. reports lecture fees from Merck, Besins and Lilly, outside the submitted work. Dr A.C., Dr D.S., Prof. C.Y.A., Prof. P.C. and M.S. have nothing to disclose.

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