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REVIEW ARTICLE

Women's vitamin D levels and IVF results: a systematic review of the literature and meta-analysis, considering three categories of vitamin status (replete, insufficient and deficient)

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ABSTRACT

To investigate the influence of vitamin D status on *in vitro* fertilisation (IVF) results, a meta-analysis of 15 cohort studies of 3711 women undergoing IVF was performed. Women were classified into three groups according their vitamin D levels (≥30 ng/mL considered replete/sufficient; 21–29 ng/mL insufficient and <20 ng/mL deficient). Three different meta-analyses were performed: (i) sufficient vs deficient; (ii) sufficient vs 'insufficient + deficient'; (iii) 'sufficient + insufficient' vs deficient. Comparing IVF outcomes in sufficient versus deficient groups (considering autologous and donor oocyte cycles together), we found women with sufficient vitamin D had significantly higher biochemical pregnancy (OR = 1.43 [1.06–1.95]), ongoing pregnancy (OR = 1.29 [1.02–1.64]), and live birth (OR = 1.74 [1.31–2.31]) rates, with a non-significant trend to a higher clinical pregnancy rate (OR = 1.31 [0.94–1.82]), whereas implantation and miscarriage rates were similar. When the meta-analysis was restricted to autologous oocytes, the parameters which had been significant in the joint analysis remained significant, and differences in implantation (OR = 1.64, [1.17–2.29]) and clinical pregnancy (OR = 1.47 [1.2–1.69]) rates became significant. No significant differences were found when considering only cycles with donor oocytes. The sufficient + insufficient vs deficient and sufficient vs 'insufficient + deficient' comparisons identified significant differences in live birth rate. The meta-analysis shows that sufficient vitamin D status is associated with better outcomes in IVF. Nonetheless, there are many demographic, geographic and clinical parameters that may be related to vitamin D status that need to be ascertained before concluding that the better results are due to the higher levels of vitamin D.

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Vitamin D; meta-analysis; IVF; live birth rate; clinical pregnancy; oocytes

Introduction

There is a growing interest in the impact of vitamin D levels on human health. It has been estimated that 20–100% of U.S., Canadian, and European elderly men and women are vitamin D deficient (Holick et al., 2011). Vitamin D deficiency has been associated with various infertility issues, such as polycystic ovary syndrome, endometriosis, myoma-induced infertility, male infertility, premature ovarian failure and poor prognosis in *in vitro* fertilisation (IVF) (Dabrowski et al., 2015). Levels of vitamin D could play a crucial role in hypothalamic-hypophyseal system regulation, anti-Müllerian hormone production, steroidogenesis and ovarian folliculogenesis, endometrial receptivity and implantation (Dabrowski et al., 2015; Paffoni et al., 2014; Zhao et al., 2018).

Many studies have analysed the relationship between vitamin D status and IVF outcomes in order to explore the possibility of increasing pregnancy and live birth rates by vitamin D administration, but results have been very mixed. Some authors have found a positive relationship (Fru et al., 2014; Garbedian et al., 2013; Ozkan et al., 2010; Paffoni et al., 2014; Polyzos et al., 2014; Rudick et al., 2012, 2014; Zhao et al., 2018), whereas others have not (Abadia et al., 2016; Aleyasin et al., 2011; Banker et al., 2017; Fabris et al., 2014, 2017; Firouzabadi et al., 2014; Trably et al., 2015; van de Vijver et al., 2016), and even a negative relationship has been reported (Anifandis et al., 2010).

The most widely employed classification of vitamin D status is that of the American Endocrine Society Clinical Practice Guideline which distinguishes three different situations according to the vitamin D levels:

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Supplemental data for this article can be accessed here.

(i) replete status or sufficiency as >29 ng/mL (≥750 nmol/L); (ii) insufficiency as levels of between 20 and 29 ng/mL (525–725 nmol/L); and (iii) deficiency as <20 ng/mL (500 nmol/L) (Holick et al., 2011). In recent years, three different meta-analyses investigating the effect of vitamin D on IVF outcomes have been published (Chu et al., 2018; Lv et al., 2016; Zhao et al., 2018). These, apart from other methodological differences, differ in their management of an 'intermediate' (insufficient) vitamin D status. In Lv et al. (2016), the insufficient group was studied together with the replete group, whereas in Chu et al. (2018) it was combined with the deficient group and in Zhao et al. (2018) it was not considered at all. Lv et al. (2016), reviewed six publications (1566 participants) and compared women with deficient vitamin D status (<20 ng/mL) with controls (≥20 ng/mL). They found higher live birth rates in women with sufficient vitamin D, although the clinical pregnancy rate was similar in the two groups. Chu et al. (2018) reviewed 11 studies (2026 patients) and compared women replete in vitamin D (>29 ng/mL) to those with deficient or insufficient levels (<30 ng/mL) and concluded that vitamin D-replete women were more likely to achieve pregnancy, clinical pregnancy and live birth than those who had deficient or insufficient levels of the vitamin. Nonetheless, some methodological problems were detected in the data retrieval and classification (Iliuta et al., 2018). Finally, Zhao et al. (2018) reviewed 9 studies (2254 patients) and compared women with sufficient levels in vitamin D to those with deficient levels, but a uniform definition of deficient levels was not used. It was concluded that deficient vitamin D was associated with a decreased probability of live birth.

Therefore, the true significance of the intermediate condition, insufficient vitamin D status (20–29 ng/mL) has yet to be assessed. The aim of this meta-analysis was to review the literature and, with the data gathered, investigate the influence of the different vitamin D status categories, alone or in combination, on IVF outcomes.

Materials and methods

PubMed, Embase and Ovid databases (from their inception to 31 October 2017) were used to identify all studies reporting on the association between vitamin D and IVF treatment outcomes, restricting the language to English, French or Spanish and following PRISMA guidelines (Moher et al., 2009) (Figure 1). The electronic search was made with the following combinations: 'vitamin D + fertility'; 'vitamin D + *in vitro* fertilization'; 'vitamin D + IVF'; 'vitamin D + assisted reproduction technologies'; 'cholecalciferol + fertility'; 'cholecalciferol + *in vitro* fertilization'; 'cholecalciferol + IVF'; 'cholecalciferol + assisted reproduction technologies'; 'calcitriol + fertility'; 'calcitriol + *in vitro* fertilization'; 'calcitriol + IVF' and 'calcitriol + assisted reproduction technologies'. The search was registered on the PROSPERO database (CRD42019128099).

Inclusion and exclusion criteria

The primary studies were included if they reported: (i) women undergoing IVF treatment; and (ii) vitamin D status checked through blood serum or follicular fluid assay. Both works in which the levels of vitamin D in serum and in follicular fluid were analysed were included in the meta-analysis, since a very close correlation between both has been described (Firouzabadi et al., 2014). Studies were excluded if they were: (i) an animal study; (ii) a review; (iii) an abstract or conference article; (iv) a letter; or (v) a study with no control or a case report.

Data extraction

The types of information extracted from all studies included were: authors and publication year, study design, number of patients, vitamin D status in blood or follicular fluid samples, timing and method of vitamin D assessment, type of oocyte used in IVF cycles (autologous vs. donated oocytes), confounder adjustments, results (number of oocytes retrieved, and rates of biochemical pregnancy, clinical pregnancy, ongoing pregnancy, live birth, and miscarriage) and conclusions (Table 1).

Study quality assessment

The Newcastle-Ottawa Quality Assessment Scale for cohort studies (Wells et al., 2014) was used by the reviewers (F.I. and R.M.) to assess the quality of the articles included (Supplementary Table 1). With this scale, a study may be awarded a maximum of one star for each numbered item within the selection (representativeness of the exposed cohort, selection of the non-exposed cohort, assessment of outcome, length of follow-up, adequacy of follow-up), and a maximum of two stars for comparability (comparability of cohorts on the basis of the design or analysis).

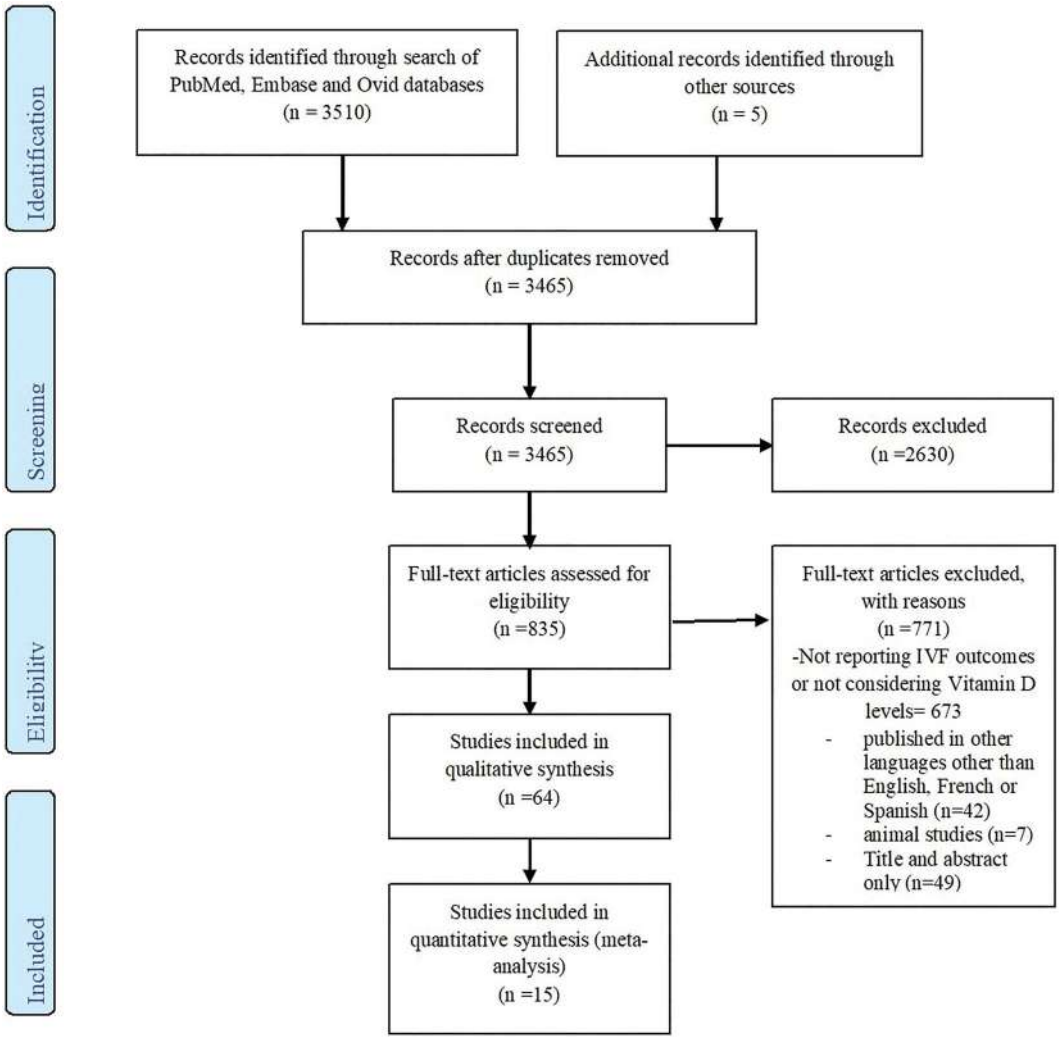

Figure 1. PRISMA diagram of the studies selection process.

The groups of vitamin D status were established according the criteria of the American Endocrine Society Clinical Practice Guideline that we have mentioned before: deficiency, insufficiency and replete status/sufficiency (Holick et al., 2011). The three groups created were analysed in three different ways: (i) replete/sufficient vs deficient; (ii) replete/sufficient vs not replete (insufficient plus deficient); and (iii) replete/sufficient plus insufficient vs deficient. The live birth rate as considered the primary outcome. Secondary outcomes were: number of oocytes retrieved and rates of implantation, biochemical pregnancy, clinical pregnancy, ongoing pregnancy, and miscarriage.

Statistical analysis

Statistical analyses were performed using Stata 15.1. The log of the ratio and its corresponding standard error were computed for each study. Forest plots were created for each outcome, showing individual study proportions with confidence intervals. The heterogeneity of the treatment effects was assessed graphically with forest plots and statistically analysed using χ^2 and I^2 tests.

Results

Our meta-analysis included 15 cohort studies of 3711 women undergoing IVF treatment from different countries: USA, Canada, Spain, France, Belgium, Italy, Greece, Iran and Turkey (Table 1). Eight of the studies were prospective, including 1503 participants (40.5%) and 7 were retrospective, including 2208 patients (59.5%). There were no prospective randomized trials. Autologous oocytes were used for IVF cycles in just under two-thirds of cases (64.3%, 2387 women from 11 studies) and donated oocytes in the others (35.7%, 1324 women from 4 studies). The bio-fluid used for vitamin D assessment was identified in all of the

Table 1. Characteristics of the studies included in the meta-analysis.

Author and year	Study type	Sample size	Source of vitamin D sample	Oocyte origin	Timing of vitamin D assessment	Method of vitamin D assessment	Vitamin D levels cut-offs	Confounders controlled for	Main results	Main conclusion
Abadia et al., 2016	CPS	100	Serum	AO	Between day 3 and day 9 of gonadotropin treatment during the first in-study ART cycle	EIA	D/Q1 = 13.5–30 ng/mL S/Q2 + Q3 + Q4 = 30.5–62.3 ng/mL	Adjustment for age, BMI, race, diet, smoking, infertility diagnosis, season of blood draw, autologous oocytes, IVF protocol	NRO=: NA IR: NA BPR (defined as serum βhCG concentration > 6 mIU/mL measured 17 d): Q1 = 24/45; Q2 = 22/41; Q3 = 28/40; Q4 = 20/42 CPR (intrauterine sac seen on ultrasound scan at 6th week of gestation): Q1 = 21/45; Q2 = 21/41; Q3 = 23/40; Q4 = 19/42 OPR (determined for the meta-analysis/MA): Q1 = 15/45; Q2 = 15/41; Q3 = 20/40; Q4 = 16/42 LBR (birth after week 24 of gestation): Q1 = 15/45; Q2 = 15/41; Q3 = 20/40; Q4 = 16/42 IR (determined for the meta-analysis/MA): Q1 = 6/45; Q2 = 6/41; Q3 = 3/40; Q4 = 3/42	Vitamin D levels may be associated with higher fertilisation rates; however, they were unrelated to the probability of having a clinical pregnancy (P-trend = 0.83) or live births after IVF (P-trend = 0.47)
Anifandis et al., 2010	CPS	101	Follicular fluid	AO	At oocytes retrieval	ECLIA	D ≤ 20 ng/mL I = 20–30 ng/mL S ≥ 30 ng/mL	Adjustment for age, BMI, IVF protocol	NRO: D = 3.9 ± 3.2; I = 5.91 ± 4.3; S = 6.14 ± 5 IR: NA BPR: NA CPR (intrauterine sac seen on ultrasound scan at 3–4th week of gestation): D = 10/31; I = 16/49; S = 3/21 OPR: NA LBR: NA MR: NA	Concentrations of vitamin D in the follicular fluid are significantly correlated with the quality of the embryos. The data suggest that high concentrations of vitamin D lead to reduced probabilities of achieving clinical pregnancy
Banker et al., 2017	CPS	291	Serum	DO	At ovulation trigger injection	CMIA	D= 20 ng/mL I + S = 20–≥30 ng/mL	NA	NRO: D = 30.74 ± 12.24; I + S = 33.33 ± 17.45 IR (the ratio of the number of gestational sacs seen on ultrasound scan after three weeks of embryo transfer to the total number of embryos transferred): D = 45/123; I + S = 29/69 BPR (not defined): D = 73/123; I + S = 44/69 CPR (ratio of women with	No significant differences were found between IVF results in the group of donors and recipients with insufficient-sufficient vitamin D levels, although the study suggests that women with sufficient levels have better results than women with

(*continued*)

Table 1. Continued.

Author and year	Study type	Sample size	Source of vitamin D sample	Oocyte origin	Timing of vitamin D assessment	Method of vitamin D assessment	Vitamin D levels cut-offs	Confounders controlled for	Main results	Main conclusion
									confirmed intrauterine sac seen on ultrasound scan to the total number of women who underwent embryo transfer): D = 65/123; I + S = 41/69 OPR (ratio of the number of pregnancies continue after 12 weeks of pregnancy to the total number of women who underwent embryo transfer): D = 45/123; I + S = 32/69 LBR: NA MR (ratio of the number of miscarriages to the total number of pregnant participants): D = 28/123; I + S = 12/69	insufficient vitamin D levels
Fabris et al., 2014	CRS	267	Serum	DO	At oocytes retrieval	ELISA	D ≤ 20 ng/mL I = 20–30 ng/mL S ≥ 30 ng/mL	Adjustment for age, number and origin of oocytes retrieved	NRO: NA IR (2 weeks after embryo transfer): D = 60/92; I = 85/134; S = 25/41 BPR: NA CPR (intrauterine sac seen on ultrasound scan after 5 weeks of embryo transfer): D = 68/92; I = 94/134; S = 29/41 OPR: D = 56/92; I = 71/134; S = 23/41 LBR: NA MR (not defined): D = 12/92; I = 23/134; S = 6/41	No significant differences were found between the groups of women with defficient, insufficient, and sufficient vitamin D levels.
Fabris et al., 2017	CRS	667	Serum	DO	NA	ELISA	D ≤ 20 ng/mL I = 20–30 ng/mL S ≥ 30 ng/mL	Adjustment for age, BMI, number and origin of oocytes retrieved	NRO: D = 16.5 ± 1.0; I = 17.1 ± 0.6; S = 17.5 ± 1.0 IR (number of intrauterine gestational sacs observed by ultrasound scan divided by the number of transferred embryos): D = 89/170; I = 304/653; S = 148/317 BPR: NA CPR (number of clinical pregnancies seen by ultrasound scan divided by	No positive correlations were found between low levels of vitamin D and unsatisfactory IVF results.

(*continued*)

Table 1. Continued.

Author and year	Study type	Sample size	Source of vitamin D sample	Oocyte origin	Timing of vitamin D assessment	Method of vitamin D assessment	Vitamin D levels cut-offs	Confounders controlled for	Main results	Main conclusion
									the number of embryo transfer cycles): D = 76/101; I = 240/373; S = 128/193 OPR (pregnancy after week 12 divided by the total number of embryo transfers): D = 54/101; I = 180/373; S = 98/193 LBR: NA MR (number of lost pregnancies before 24 weeks of gestation divided by the number of clinical pregnancies): D= 22/76; I= 60/240; S= 30/128	
Firouzabadi et al., 2014	CPS	221	Follicular fluid and serum	AO	At oocytes retrieval	ELISA	D $\leq$ 10 ng/mL I = 10–30 ng/mL S $\geq$ 30 ng/mL	Adjustment for age, BMI, hormones, number of follicles and of TE	NRO: NA IR (not defined by the authors): D = 9/50; I = 24/155; S= 3/16 BPR (undefined): D = 23/50; I = 83/155; S = 9/16 CPR (intrauterine gestational sac with foetal heartbeat present- no data on the week): D = 23/50; I= 47/155; S = 4/16 OPR: NA LBR: NA MR: NA	No positive correlations were found of vitamin D levels in follicular fluid and serum with clinical pregnancy rate
Franasiak et al., 2015	CRS	517	Serum	AO	At ovulation trigger injection	ELISA	D $\leq$ 20 ng/mL I = 20–30 ng/mL S $\geq$ 30 ng/mL	Adjustment for age, BMI, season of blood sample draw, number of TE	NRO: NA IR: NA BPR (pregnancy test two weeks after embryo transfer): D = 163/206; I = 162/215; S = 74/96 CPR (gestational sac with presence of foetal heartbeat- no data on the week): D = 144/206; I = 151/215; S = 64/96 OPR (presence of a foetal heartbeat after the first trimester of pregnancy or live births at the end of the study, without specifying the number of live births): D = 131/206;	No association was found between vitamin D levels and pregnancy outcomes.

(*continued*)

Table 1. Continued.

Author and year	Study type	Sample size	Source of vitamin D sample	Oocyte origin	Timing of vitamin D assessment	Method of vitamin D assessment	Vitamin D levels cut-offs	Confounders controlled for	Main results	Main conclusion
									I = 133/215; S = 60/96 LBR: NA MR (pregnancy loss after a positive test, but before the gestational sac was seen by the ultrasound scan): D = 32/206; I = 29/215; S = 14/96	
Fru et al., 2014	CRS	102	Serum	AO	NA	NA	D ≤ 20 ng/mL I = 20–30 ng/mL S ≥ 30 ng/mL	NA	NRO: NA IR: NA BPR: NA CPR (not defined): D = 6/18; I = 24/47; S = 37/58 OPR (undefined): D = 5/18; I = 15/47; S = 25/58 LBR (undefined): D= 5/18; I = 15/47; S = 25/58 MR (calculated as the difference between the clinical pregnancy rate and the number of live births): D = 1/18; I = 9/47; S = 12/58	A positive correlation was found between higher vitamin D levels and higher probability of positive pregnancy test. In general, higher rates of clinical pregnancy were found in the group with a sufficient vitamin D level
Garbedian et al., 2013	CPS	173	Serum	AO	Before oocytes retrieval	NA	D = 30 ng/mL S ≥ 30 ng/mL	Adjustment for age, BMI, number of TE	NRO: D-I = 12.6 ± 7.4; S = 12.7 ± 6.6 IR (undefined): D + I = 24/95; S = 27/78 BPR: NA CPR (gestational sac with presence of foetal heartbeat- no data on the week): D-I = 33/95; S = 41/78 OPR: NA LBR: NA MR: NA	Women with sufficient levels of vitamin D level were found to be significantly more likely to achieve clinical pregnancy following IVF treatment.
Ozkan et al., 2010	CPS	84	Follicular fluid and serum	AO	At ovulation trigger injection	NA	D ≤ 20 ng/mL I = 20–30 ng/mL S ≥ 30 ng/mL	Adjustment for age, BMI, race, number of TE	NRO: NA IR: NA BPR (two weeks following embryo transfer): D = 3/23; I = 4/30; S = 8/31 CPR (gestational sac with presence of foetal heartbeat- no data on the week): D = 5/23; I = 6/30; S = 15/31 OPR: NA	Higher rates of clinical pregnancy were found in the groups with higher levels of vitamin D

(*continued*)

Table 1. Continued.

Author and year	Study type	Sample size	Source of vitamin D sample	Oocyte origin	Timing of vitamin D assessment	Method of vitamin D assessment	Vitamin D levels cut-offs	Confounders controlled for	Main results	Main conclusion
Paffoni et al., 2014	CPS	335	Serum	AO	Pre ART cycle, no further data available	ECLIA	D ≤ 20 ng/mL I = 20–30 ng/mL S ≥ 30 ng/mL	Adjustment for age, BMI, race, duration of IVF treatment, hormones	LBR: NA MR: NA NRO (the data obtained comes from the group of women deficient in vitamin D (<20 ng / mL) and the sum of insufficient and sufficient groups (≥20 ng / mL): D = 8.1 ± 4.2; I + S = 7.9 ± 4.2 IR (number of viable embryos divided by the number of transferred embryos): D = 37/154; I + S = 70/181 BPR (two weeks after embryo transfer): D = 34/154; I = 36/117; S = 25/64 CPR (gestational sac with presence of foetal heartbeat- no data on the week): D = 30/154; I = 33/117; S = 23/64 OPR (undefined): D = 29/154; I = 28/117; S = 19/64 LBR (undefined): D = 29/154; I = 28/117; S = 19/64 MR rate (calculated as the difference between the clinical pregnancy and live birth rates): D = 1/154; I = 5/117; S = 4/64	Clinical pregnancy rate and the implantation rate were found to be significantly lower in the vitamin D deficient group.
Polyzos et al., 2014	CRS	368	Serum	AO	At ovulation trigger injection	ELISA	D ≤ 20 ng/mL I= 20–30 ng/mL S ≥ 30 ng/mL	Adjustment for age, BMI, race, infertility diagnosis, number and type of previous IVF cycles, season of blood analysis	NRO: D = 12.1; I + S = 12.0 IR: NA BPR (two weeks after embryo transfer): D = 124/239; I + S = 86/129 CPR (gestational sac with presence of foetal heartbeat seen by ultrasound scan at week 5 after embryo transfer): D = 98/239; I + S = 70/129 (I = 49/92, S = 21/37) OPR (undefined): D = 78/239; I + S = 61/129 LBR (undefined): D = 78/239; I + S = 61/129	Significantly lower rates were found in the group of women with low vitamin D levels.

(*continued*)

Table 1. Continued.

Author and year	Study type	Sample size	Source of vitamin D sample	Oocyte origin	Timing of vitamin D assessment	Method of vitamin D assessment	Vitamin D levels cut-offs	Confounders controlled for	Main results	Main conclusion
									MR (calculated as the difference between the clinical pregnancy and live birth rates): D = 20/239; I + S = 9/129	
Rudick et al., 2012	CRS	188	Follicular fluid	AO	Pre ART cycle, no further data available	ELISA	D ≤ 20 ng/mL I = 20–30 ng/mL S ≥ 30 ng/mL	Adjustment for age, BMI, race, infertility diagnosis, number and type of previous IVF cycles, NRO and number of TE	NRO: D = 17; I = 14; S = 11 IR (definition not available, and being calculated as the average between the three ethnic groups: non-Hispanic, Hispanic, Asian white): D = 9/39; I = 16/70; S = 18/79 BPR: NA CPR (gestational sac with presence of foetal heartbeat seen by ultrasound scan at week 5 after embryo transfer): D = 14/39; I = 29/70; S = 34/79 OPR (undefined): D = 11/39; I = 22/70; S = 26/79 LBR (undefined): D = 11/39; I = 22/70; S = 26/79 MR (pregnancy loss after a positive test, but before the gestational sac is seen by ultrasound scan): D = 3/39; I = 7/70; S = 8/79	Vitamin D deficiency was associated with a lower pregnancy rate in Caucasian women, but not in Asian women, probably due to their lower success rate in IVF treatments
Rudick et al., 2014	CRS	99	Serum	DO	Pre ART cycle, no further data available	ELISA	D ≤ 20 ng/mL I = 20–30 ng/mL S ≥ 30 ng/mL	Adjustment for age, BMI, race, IVF protocol, number of retrieves and of TE	NRO: D = 27.3; I = 25.5; S = 23.9 IR: NA BPR: NA CPR (gestational sac with presence of foetal heartbeat seen by ultrasound scan at week 5 after embryo transfer): D = 9/26; I = 16/38; S = 26/35 OPR (undefined): D = 8/26; I = 13/38; S = 20/35 LBR (undefined): D = 8/26; I = 13/38; S = 20/35 MR (pregnancy loss after a positive test, but before	Non-replete levels of vitamin D were correlated with lower pregnancy rates

(*continued*)

Table 1. Continued.

Author and year	Study type	Sample size	Source of vitamin D sample	Oocyte origin	Timing of vitamin D assessment	Method of vitamin D assessment	Vitamin D levels cut-offs	Confounders controlled for	Main results	Main conclusion
									the gestational sac is seen by ultrasound scan): D = 1/26; I = 3/38; S = 6/35	
Trably et al., 2015	CPS	198	Serum	AO	During the follicular block phase	NA	I ≤ 20 ng/mL S ≥ 20 ng/mL	Adjustment for age, BMI, race, infertility diagnosis	NRO: NA IR: NA BPR (beta-hCG concentration > 100 U/L): I = 51/169; S = 8/29 CPR (gestational sac with presence of foetal heart beat in week 7 of amenorrhea): I = 35/169; S = 4/29 OPR (undefined): I = 35/169; S = 4/29 LBR: NA MR (not ongoing pregnancy): I = 16/169; S = 4/29	No correlations were found between vitamin D concentrations and pregnancy outcomes after IVF treatment

Abbreviations. CPS: cohort prospective study; CRS: cohort retrospective study; AO: autologous oocytes; DO: donor oocytes; TE: transferred embryos; NA: no available data; EIA: enzyme immunosorbent assay; ECLIA: electrochemiluminescence immunoassay; CMIA: chemiluminescent microparticle immunoassay; ELISA: enzyme-linked immunosorbent assay; D: vitamin D deficiency; I: insufficiency; S: sufficiency; BPR: biochemical pregnancy rate; CPR: clinical pregnancy implantation rate; MR: miscarriage rate.

studies included and women were classified according to their vitamin D status. Eleven studies analysed only blood samples, two only follicular fluid and two included both blood and follicular fluid samples. Our meta-analysis found a high prevalence of vitamin D inadequacy in women undergoing IVF treatment studied, with 33.7% of women with levels classed as deficient (1250/3711) and 38.5% (1429/3711) as insufficient and only 27.8% (1032/3711) sufficient.

*Comparison between vitamin d-sufficient and -deficient groups (**Supplementary Table 2**)*

Number of oocytes retrieved

Eight of the 15 studies analysed provided data on the number of oocytes retrieved during the IVF cycles, 7 using the mean ± standard deviation as data analysis measures and one (Rudick et al., 2014) the median and interquartile range. We carried out a meta-analysis of continuous data, using the Cohen method to estimate the standardized mean difference (SMD) with a random effects model (Figure 2). This did not show a statistically significant association between the number of oocytes retrieved and vitamin D status probably due to the significant heterogeneity in the data (I^2 89.7%).

Implantation rate

The definition of implantation rate varied across the seven studies (1504 participants) that provided data on IVF. Banker et al. (2017) and both studies by Fabris et al. (2014 and 2017) defined implantation rate as the number of gestational sacs observed by ultrasound in the second to third week divided by the total number of transferred embryos, and Paffoni et al. (2014) specify that they calculated 'the number of viable embryos divided by the number of transferred embryos', while the other authors did not provide a definition. The odds ratio obtained by comparing the two groups for this variable was 1.18 [0.85–1.63], did not reaching statistical significance (Figure 3(a)).

Biochemical pregnancy (positive pregnancy test)

Seven of the 15 analysed studies (1398 participants) gave data on the positive biochemical pregnancy (positive pregnancy test) rate. Four groups (Franasiak et al., 2015; Ozkan et al., 2010; Paffoni et al., 2014; Polyzos et al., 2014) defined biochemical pregnancy as a positive pregnancy test two weeks after embryo transfer, and Trably et al. (2015) defined it as a concentration of beta-hCG greater than 100 U/L. In our analysis, the resulting biochemical pregnancy rate was

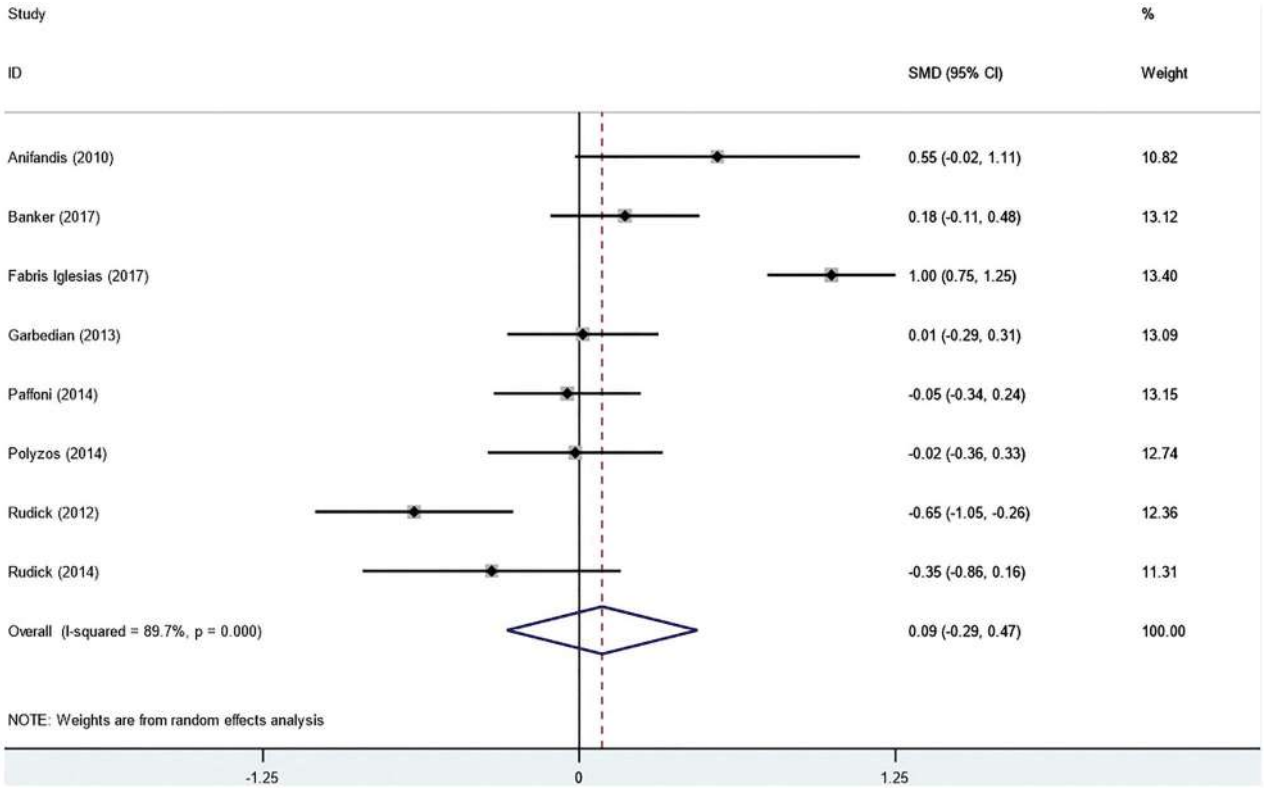

Figure 2. Meta-analysis of the studies regarding the number of oocytes retrieved (vitamin D-deficient vs. -sufficient groups). There is no statistically significant association between vitamin D levels and the number of oocytes recovered after IVF cycles.

48.8% in the deficient group and 58.52% in the sufficient group. A significant positive relationship was found between higher vitamin D levels and better IVF outcomes (OR 1.43 [1.06–1.95] (Figure 3(b)).

Clinical pregnancy

All 15 studies provided data on clinical pregnancy (2385 participants). Six groups defined clinical pregnancy as a gestational sac with the presence of foetal heartbeat seen by ultrasound in the fifth week after embryo transfer (Abadia et al., 2016; Fabris et al., 2014; Polyzos et al., 2014; Rudick et al., 2012, 2014; Trably et al., 2015). Anifandis et al. (2010) defined it as an intrauterine sac seen by ultrasound in the third to fourth week after hCG administration, Fru et al. (2014) did not provide a definition and all other authors defined it as a gestational sac with a foetal heartbeat present, without specifying the gestational week. The rate of clinical pregnancy was 45.14% in the deficient group and somewhat higher (54.7%) in the sufficient group. Comparing the patients in the deficient and sufficient groups, we obtained an OR of 1.31 [0.94–1.82], with significant variation in the OR attributable to the high heterogeneity (I2 61.8%) (Figure 4(a)).

Ongoing pregnancy rate

Eleven of the 15 studies included in the meta-analysis (2132 participants) provided data on ongoing pregnancy rate. Only three authors defined the ongoing pregnancy rate: two as pregnancy after the twelfth week (Banker et al., 2017; Fabris et al., 2017) and one (Franasiak et al., 2015) as the presence of a foetal heartbeat beyond the first trimester divided by the number of women with transfers made. The ongoing pregnancy rate in the deficient group was lower than that in the sufficient group: 38.5% vs. 45.5%, with an OR of 1.29 [1.02–1.64], demonstrating once more a beneficial association between higher vitamin D levels and better IVF outcomes (Figure 4(b)).

Live birth rate

Data were provided on live births in six articles (1013 participants). Abadia et al. (2016) defined live births as the birth of a neonate on or after 24 weeks of gestation, while the other authors did not provide a definition. We found live birth rates of 28.0% in the vitamin D-deficient group and 41.0% in the vitamin D-sufficient group, these outcomes being statistically significant (OR 1.74 [1.31–2.31]) (Figure 5(a)).

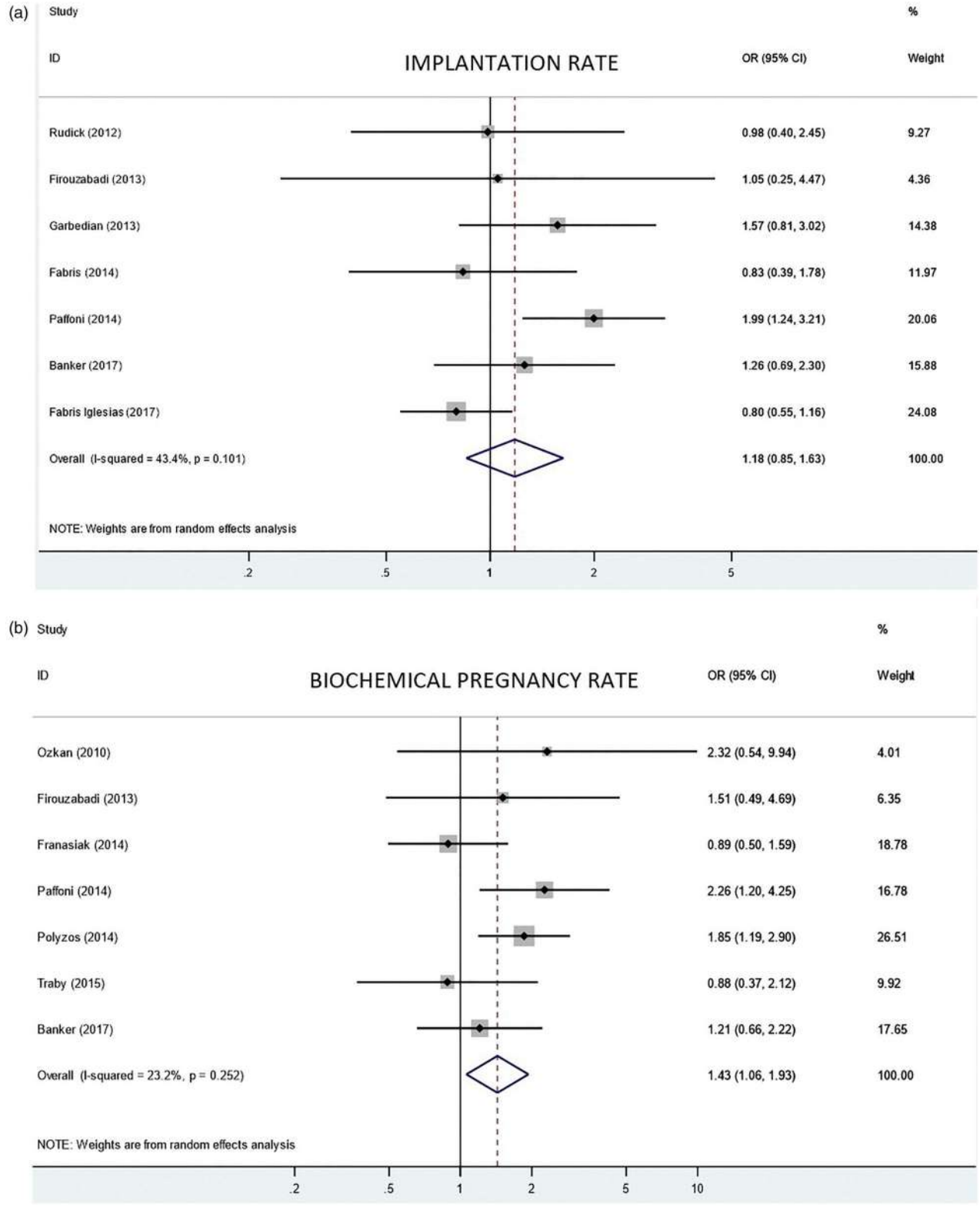

Figure 3. Comparison between implantation rate and biochemical pregnancy rate in the vitamin D Deficient vs. Sufficient group. No statistical significance (OR = 1,18 [0.08–1.63]) in implantation rate (a); Statistically significant differences (OR = 1.43 [1.06–1.95]) in biochemical pregnancy rate (b).

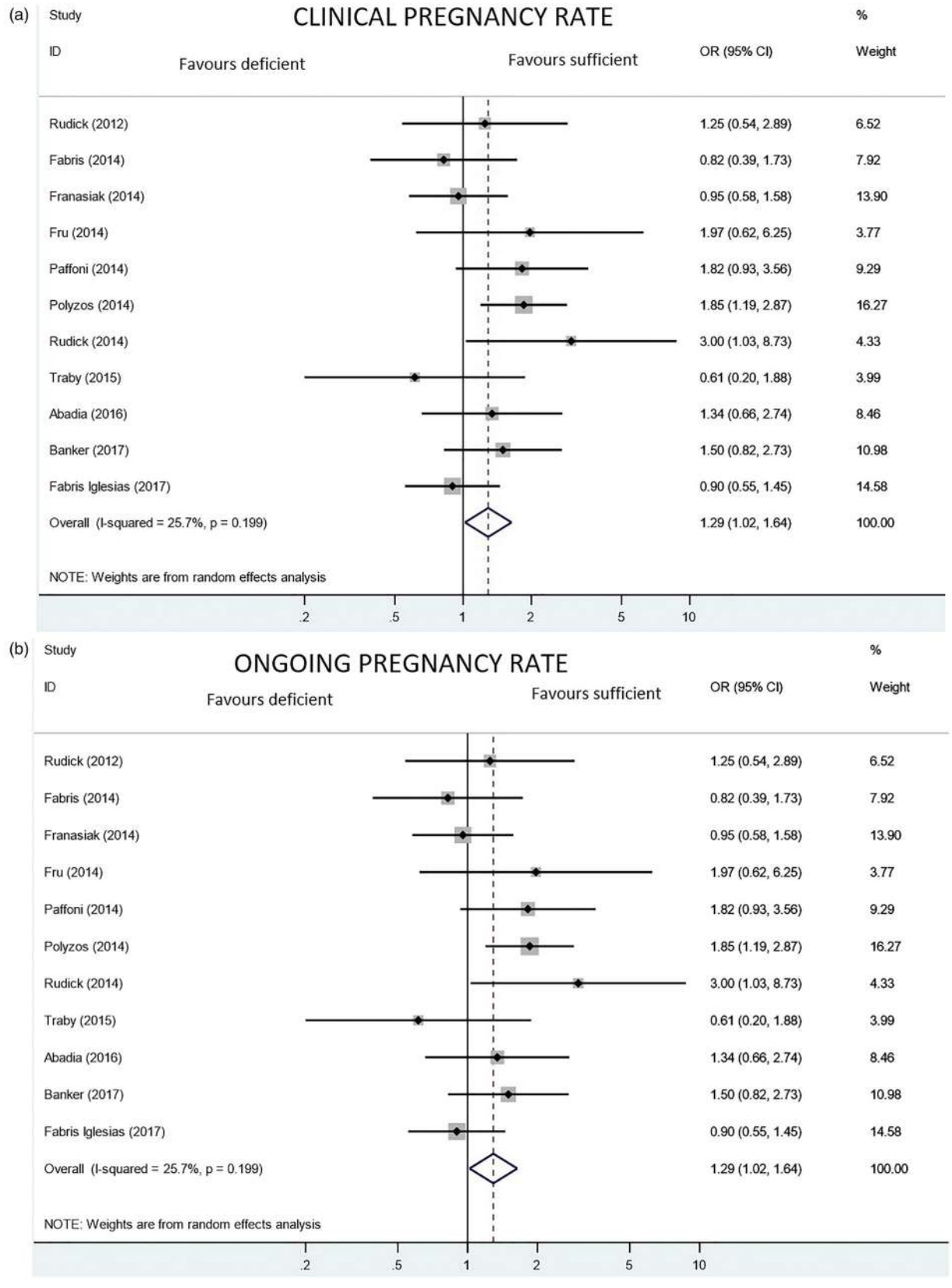

Figure 4. Comparison between the clinical pregnancy rate and ongoing pregnancy rate in the vitamin D Deficient vs. Sufficient group. No significant differences (OR = 1.31 [0.94–1.82]) in clinical pregnancy rate (a); Statistically significant differences (OR = 1.29 [1.02–1.64]) in ongoing pregnancy rate (b).

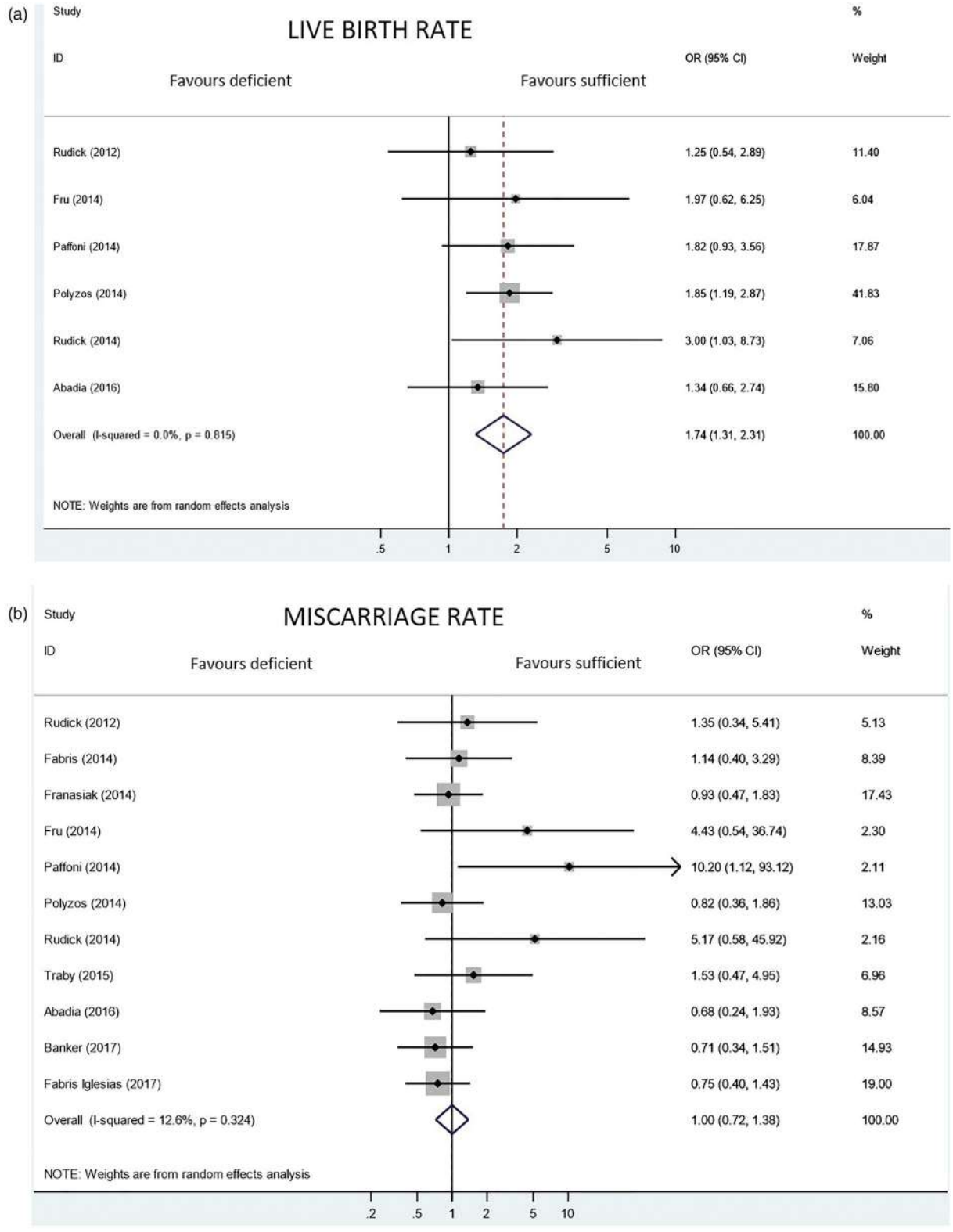

Figure 5. Comparison between the live birth rate and miscarriage rate in the vitamin D Deficient vs. Sufficient group. Statistically significant differences (OR = 1.74 [1.31–2.31]) in live birth rate (a); No significant differences (OR = 1.00 [0.72–1.38]) in miscarriage rate (b).

Miscarriage rate

Eleven of the 15 studies included provided data on miscarriage rate (2042 participants). Three of the studies defined the miscarriage rate as pregnancy loss after a positive test, but before the gestational sac is seen by ultrasound (Franasiak et al., 2015; Rudick

Table 2. Odds ratio and 95% confidence intervals of the meta-analysis of the IVF outcomes when comparing the origin of the oocytes in vitamin D-sufficient vs. -deficient groups, for all variables studied.

Oocyte origin	Implantation rate	Biochemical pregnancy rate	Clinical pregnancy rate	Ongoing pregnancy rate	Live birth rate	Miscarriage rate
Autologous	1.64 [1.17–2.29]	1.53 [1.18–1.93]	1.47 [1.2–1.79]	1.36 [1.1–1.69]	1.71 [1.31–2.25]	1.22 [0.86–1.73]
Donor	NA	NA	1.40 [0.74–2.61]	NA	NA	NA

NA: not available, since there was only one published study.

et al., 2012, 2014). The earlier study of Fabris et al. (2014) did not give a definition, whereas in their later study (Fabris et al., 2017), this group defined it as the number of pregnancies lost before 24 weeks of gestation divided by the number of clinical pregnancies. Banker et al. (2017) define it as the ratio of the number of miscarriages to the total number of pregnant participants and Trably et al. (2015) pregnancies that do not progress. As sufficient data were available in some of the other studies (Abadia et al., 2016; Fru et al., 2014; Paffoni et al., 2014; Polyzos et al., 2014.), the miscarriage rate has been calculated, using the difference between the numbers of clinical pregnancies and live births. Comparing all these data, similar outcomes were found in the vitamin D-deficient and -sufficient groups: 11.9% vs. 13.6%, differences not being significant (OR 1.00 [0.72–1.38]) (Figure 5(b)).

IVF outcomes according to oocyte source

All 15 studies have been analysed according to the origin of the oocytes: autologous or from donors (Table 2). Regarding autologous oocytes, there were 11 studies with 1705 participants (Abadia et al., 2016; Anifandis et al., 2010; Firouzabadi et al., 2014; Franasiak et al., 2015; Fru et al., 2014; Garbedian et al., 2013; Ozkan et al., 2010; Paffoni et al., 2014; Polyzos et al., 2014; Rudick et al., 2012; Trably et al., 2015), although not all of them provide data for all variables studied. Overall, 63% of women were vitamin D deficient (1069/1705) and 37% vitamin D sufficient (636/1705). All the IVF outcome parameters were significantly better in the sufficient group (implantation rate, OR 1.64 [1.17–2.29]; biochemical pregnancy rate, OR 1.47 [1.2–1.79]; clinical pregnancy rate, OR 1.47 [1.2–1.79] (ongoing pregnancy rate, OR 1.36 [1.1–1.69]; and live birth rate, OR 1.71 [1.31–2.25]), with the exception of the miscarriage rate, which was similar.

On the other hand, there were four studies using oocytes from donors (Banker et al., 2017; Fabris et al., 2014, 2017; Rudick et al., 2014) with 680 participants, 50.3% of them being vitamin D deficient (342/680) and 49.7% having sufficient levels (338/680).

Only one study (Fabris et al., 2017) reported implantation and pregnancy rates according donor status. Three studies considered vitamin D receptor status (Banker et al., 2017; Fabris et al., 2014; Rudick et al., 2014) but only two considered the differences between deficient and sufficient women (Fabris et al., 2014; Rudick et al., 2014). The clinical pregnancy rate was reported in both papers, and the meta-analysis was 72.37% (55/76) among sufficient women vs 65.25% (77/118) in deficient women, OR 1.40 [0.74–2.61]. In the remaining parameters meta-analysis could not be performed since none was reported in at least two studies.

Comparison between vitamin D-sufficient vs 'insufficient + deficient' groups

As when comparing sufficient with deficient groups, the statistical comparison of sufficient with 'not sufficient' (insufficient and deficient) groups revealed a significant association between live birth rate and higher vitamin D levels (OR 1.53 [1.12–2.09]), with an I2 of 0 (Figure 6(a)). On the other hand, differences between these groups in rates of implantation, biochemical pregnancy, clinical pregnancy, ongoing pregnancy and miscarriage did not reach statistical significance (see Supplementary Table 3 and Supplementary Figures 1 & 2).

Comparison between vitamin D 'sufficient and insufficient' vs deficient group

The results of comparing the 'not deficient' and deficient groups were very similar to those of comparing sufficient and 'not sufficient' groups. The live birth rate was significantly higher in the 'sufficient and insufficient' group than in the deficient group (OR 1.59 [1.22–2.07], I2 of 0%) (Figure 6(b)), but other outcomes were similar (see Supplementary Table 4 and Supplementary Figures 3 & 4).

Discussion

Vitamin D deficiency/insufficiency is highly prevalent in infertile women, as well as in the general population (Holick et al., 2011). It has been suggested that lower levels in vitamin D could impair IVF results. As the correction of vitamin D deficiency by exogenous

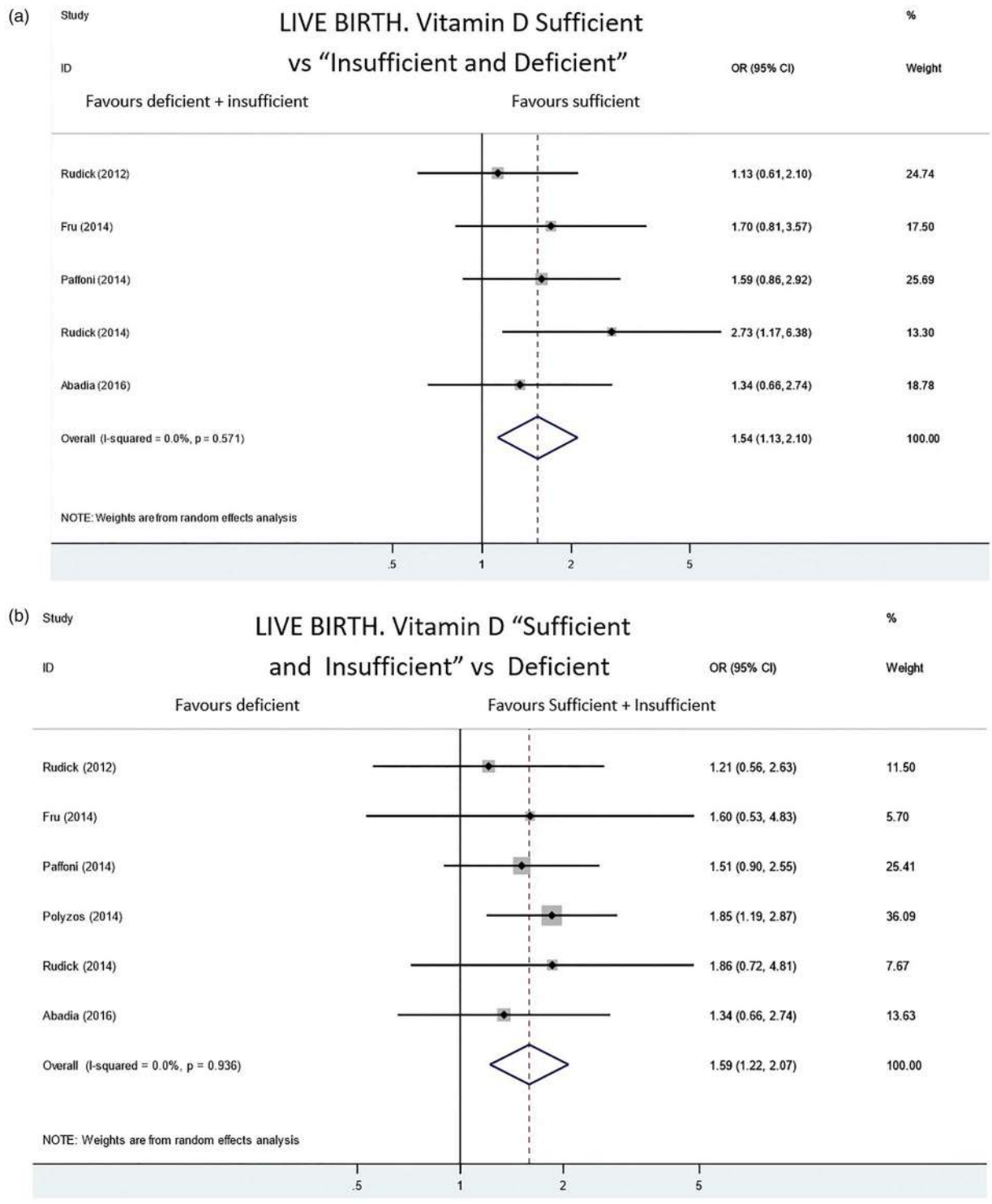

Figure 6. Comparison of Live Birth Rates after the insufficient group is added to the sufficient or deficient group. Statistically significant differences (OR = 1.53 [1.12–2.09]) comparing vitamin D Sufficient vs Insufficient and Deficient status (6a); Statistically significant differences (OR = 1.59 [1.22–2.07]) comparing vitamin D 'Sufficient and Insufficient' vs Deficient status.

administration is straightforward, knowledge of the association could allow us to improve IVF outcomes.

For our meta-analysis, we retrieved 15 publications, including a total of 3711 patients, notably more than the three previous meta-analysis also focussing on vitamin D status and IVF results which analysed 6, 9 and 11 publications, with a total of 1566, 2254 and 2026 patients respectively (Chu et al., 2018; Lv et al., 2016; Zhao et al., 2018). We considered three different comparisons, between women with sufficient, insufficient, and deficient vitamin D levels, seeking to detect any possible association between vitamin D status and

IVF outcomes, and notably, including a focus on those with insufficient levels (i.e. the intermediate condition). Although the methodology we employed is not the same, our results are consistent with those of the aforementioned meta-analyses (Chu et al., 2018; Lv et al., 2016; Zhao et al., 2018).

There are great discrepancies between the conclusions of the studies included. Although the majority of authors have postulated that there is a positive association between higher vitamin D levels and the best IVF outcomes, most have failed to demonstrate statistically significant differences (Abadia et al., 2016; Banker et al., 2017; Fabris et al., 2014, 2017; Firouzabadi et al., 2014; Franasiak et al., 2015; Trably et al., 2015). Anifandis et al. (2010) even found a negative association between the replete follicular fluid vitamin D status and the quality of embryos, their data suggesting that high concentrations of vitamin D lead to reduced probabilities of obtaining clinical pregnancy. On the other hand, numerous others (Fru et al., 2014; Garbedian et al., 2013; Ozkan et al., 2010, Paffoni et al., 2014; Polyzos et al., 2014; Rudick et al., 2012, 2014) have found a positive association between serum or follicular fluid vitamin D status and IVF outcomes. In general, higher clinical pregnancy rates have been found in vitamin D-sufficient groups compared to those with deficient/insufficient status.

Our search of the literature revealed a great methodological heterogeneity regarding vitamin D in IVF. The studies included differed in terms of: ethnic group, geographical location, IVF protocol and timing of the sample retrieval and its type (serum, follicular fluid). Moreover, there were differences in the laboratorial methods to assess vitamin D, as well as in the calculation of the miscarriage and implantation rates, amongst others. This could represent a methodological weakness of our study. Nonetheless, as suggested by Chu et al. (2018), such heterogeneity has the advantage of its more realistic applicability in the general population. However, it has to be highlighted that there was no randomized prospective study in our meta-analysis. Indeed, the majority of studies reviewed did not gather or report data to perform an adjusted analysis controlling for possible confounding factors such as age, social status, ethnic group, body mass index, smoking, seasonal effects or disorders that have been linked with vitamin D status, such endometriosis and polycystic ovarian syndrome (Dabrowski et al., 2015). Since most of the aforementioned parameters can be associated with IVF outcome, it was not possible to ascertain the independent influence of vitamin D status. Although the retrieval of the samples has been carried out at different moments of the IVF cycle, Chu et al. (2018) suggest that the difference in the timing of sample collection is not important since vitamin D status tends not to fluctuate over time; except when the deficit is treated medically (Anagnostis et al., 2013). Eleven studies measured vitamin D only in serum samples, two studies only in follicular fluid exclusively and another two in both biofluids. Some of these authors (Anifandis et al., 2010; Firouzabadi et al., 2014; Ozkan et al., 2010) found an association between vitamin D serum and follicular fluid status, in consequence, the different origin of the sample should not be considered a confounding factor.

Regarding the different ethnic groups, Rudick et al. (2012) found a negative association between pregnancy rates and vitamin D in Asian women, compared to Caucasian women, probably due to their lower success rate in IVF treatments. The same conclusion is supported by other authors, who indicate Asian or black ethnicity as a negative prognostic factor for IVF outcomes (Dhillon et al., 2016).

The comparison of IVF outcomes in vitamin D-sufficient versus deficient women (studying together autologous and donor oocytes) showed significantly higher biochemical pregnancy rates (OR 1.43 [1.06–1.95]), as well as ongoing pregnancy rates (OR = 1.29 [1.02–1.64]), and live birth rates (OR 1.74 [1.31–2.31]), with a non-significant trend to higher clinical pregnancy rate (OR = 1.31 [0.94–1.82]), while implantation and miscarriage rates were similar.

Eleven of the 15 studied publications used autologous oocytes for the IVF cycles (2387 women) and 4 of them used donor oocytes (1324 women). When a split meta-analysis was made according oocyte source, the results were very different. When the meta-analysis was restricted to autologous oocytes, the parameters which were statistically significant in the joint analysis (biochemical pregnancy, ongoing pregnancy and live birth rates) remained significant (OR = 1.53 [1.18–1.93]; OR = 1.71 [1.31–2.25] and OR 1.71; [1.31–2.25]), and implantation (OR = 1.64, [1.17–2.29]) and clinical pregnancy (OR = 1.47 [1.2–1.69]) rates became significant.

Concerning cycles performed with donor oocytes, one study focussed on vitamin D levels in donors, reporting that pregnancy rates were similar in recipients (Fabris et al., 2017). Regarding the remaining three, the only parameter which could be subjected to meta-analysis was clinical pregnancy rate, and there were non-significant differences (OR 1.40; [0.74–2.61]).

It has been speculated regarding an influence of vitamin D on the endometrium, rather than on oocyte quality (Abedi et al., 2019). In agreement with this, in a very recent small double-blind randomized trial administering vitamin D 6 weeks before ICSI, no effects were observed on oocyte or embryo parameters, although better endometrium quality (as assessed by ultrasound) and better clinical pregnancy rates were reported in the group that received vitamin D (Abedi et al., 2019). However in our meta-analysis there was only one study focussing on donor levels, whereas the heterogeneity of reporting data in the three recipient studies precluded their analysis.

It has been suggested that vitamin D could influence endometrial receptivity by up-regulating HOXA10 in endometrial stromal cells (Du et al., 2005). HOXA10 is a homeobox-containing transcription factor which is essential for endometrial receptivity and decidualization (Taylor et al., 1998). On the other hand, in one study performed with euploid embryos, no differences were observed in pregnancy rates (Franasiak et al., 2015). It has been suggested that the potential effect of a low vitamin D level is mitigated once embryos are cultured to the blastocyst stage and proven to be chromosomally normal (Franasiak et al., 2015).

To assess the reproductive significance of the 'intermediate' vitamin D status (insufficient), we performed two different meta-analyses: one studying the insufficient condition together with the replete/sufficient condition, and another grouping the insufficient condition with the deficient condition. The results were fairly similar in both analyses: significance was reached regarding live birth rates in both cases (OR 1.53 [1.12–2.09] in sufficient vs not sufficient and OR 1.59 [1.22–2.07] in not deficient vs deficient). Significance was not reached for the other variables studied, although a trend to better IVF outcomes was observed associated with higher vitamin D levels.

Our meta-analysis shows better reproductive outcomes (implantation, clinical and ongoing pregnancy, and live birth rates) in IVF cycles associated with the sufficient vitamin D status when compared to deficient status. Better live birth rates were observed in the group of women with insufficient vitamin D together with those with sufficient levels than in the group with deficient levels, as well as in women with sufficient levels than the group with insufficient and deficient levels. Nonetheless, taking into account the great number of parameters linked to vitamin D status (age, ethnicity, season, social class, smoking, body mass index, associated conditions), the independent relevance of vitamin D remains to be ascertained.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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