



Clinical trial results:

Vitamin D Supplementation on Assisted Reproduction Technology (ART) outcomes: a randomized clinical controlled trial and an investigation of the involved biological mechanisms

Summary

EudraCT number	2015-004233-27
Trial protocol	IT
Global end of trial date	31 December 2019

Results information

Result version number	v1 (current)
This version publication date	23 July 2021
First version publication date	23 July 2021
Summary attachment (see zip file)	Manuscript AJOG (1-s2.0-S0002937821004646 AJOG vitamin d.pdf)

Trial information

Trial identification

Sponsor protocol code	RF-2013-02358757
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	SUNDRO: -

Notes:

Sponsors

Sponsor organisation name	FONDAZIONE IRCCS CA' GRANDA OSPEDALE MAGGIORE POLICLINICO
Sponsor organisation address	via Sforza 35, Milan, Italy,
Public contact	U.O.S.D. CENTRO P.M.A., FONDAZIONE IRCCS CA' GRANDA OSPEDALE MAGGIORE POLICLINICO, 0039 0255036582, centrosterilita@policlinico.mi.it
Scientific contact	U.O.S.D. CENTRO P.M.A., FONDAZIONE IRCCS CA' GRANDA OSPEDALE MAGGIORE POLICLINICO, 0039 0255036582, centrosterilita@policlinico.mi.it

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

the study aims at determining the potential benefits of vitamin D supplementation in improving clinical pregnancy rate in women undergoing ART

Protection of trial subjects:

no particular concerns regarding pain or distress related to the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 630
Worldwide total number of subjects	630
EEA total number of subjects	630

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	630
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Women undergoing IVF with or without intracytoplasmic sperm injection (ICSI) at the infertility units of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and IRCCS San Raffaele Scientific Institute between October 2016 and January 2019 were considered for study entry. Recruitment was consecutive.

Pre-assignment

Screening details:

Evaluated 2450 subjects; Eligible 1128 subjects; enrolled 630 subjects.

Period 1

Period 1 title	first (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Vitamin D

Arm description: -

Arm type	Experimental
Investigational medicinal product name	DBase
Investigational medicinal product code	36635035
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Supplementation was given as a single administration of oral 600,000 IU of vitamin D3 to ensure maximal adherence. This modality is expected to properly maintain peripheral levels of vitamin D above 30 ng/mL for 3 months,

Arm title	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo olive oil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

Placebo was given as a single administration of oral olive oil.

Number of subjects in period 1	Vitamin D	Placebo
Started	308	322
Completed	308	322

Baseline characteristics

Reporting groups

Reporting group title	Vitamin D
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Vitamin D	Placebo	Total
Number of subjects	308	322	630
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	35	35	
inter-quartile range (Q1-Q3)	32 to 37	33 to 37	-
Gender categorical Units: Subjects			
Female	308	322	630
Male	0	0	0

Subject analysis sets

Subject analysis set title	Pregnancy rate
Subject analysis set type	Full analysis
Subject analysis set description: IVF cycle outcome in the 2 study groups	
Subject analysis set title	Supplemented
Subject analysis set type	Intention-to-treat
Subject analysis set description: women receiving vitamin D	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Women receiving placebo	

Reporting group values	Pregnancy rate	Supplemented	Placebo
Number of subjects	630	308	322
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female	630	308	322
Male	0	0	0

End points

End points reporting groups

Reporting group title	Vitamin D
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Pregnancy rate
Subject analysis set type	Full analysis
Subject analysis set description: IVF cycle outcome in the 2 study groups	
Subject analysis set title	Supplemented
Subject analysis set type	Intention-to-treat
Subject analysis set description: women receiving vitamin D	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Women receiving placebo	

Primary: Pregnancy rate

End point title	Pregnancy rate
End point description:	
End point type	Primary
End point timeframe: 5 weeks after last treatment	

End point values	Vitamin D	Placebo	Pregnancy rate	Supplemented
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	308	322	573	322
Units: patients				
Pregnancy	113	130	243	113

End point values	Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	308			
Units: patients				
Pregnancy	130			

Statistical analyses

Statistical analysis title	Clinical pregnancy rate
Statistical analysis description: cumulative clinical pregnancy rate	
Comparison groups	Vitamin D v Placebo
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.11

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Only maternal events occurring within 3 months from randomization were considered because a single dose of 600,000 IU is expected to raise peripheral levels for no more than 3 months.

Adverse event reporting additional description:

Given the well-known pharmacologic and safety profile of vitamin D3, we did not deem necessary a strict monitoring of the included women, and only severe adverse events were recorded (death, life-threatening conditions, new or prolonged hospitalization, persistent or relevant disability, or congenital anomalies).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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Reporting groups

Reporting group title	vitamin D
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Reporting group description: -

Reporting group title	placebo
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Given the well-known pharmacologic and safety profile of vitamin D3,17,22 we did not deem necessary a strict monitoring of the included women, and only severe adverse events were recorded (death, life-threatening conditions, new or prolonged hospitalization, persistent or relevant disability, or congenital anomalies).

Serious adverse events	vitamin D	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 308 (0.00%)	2 / 322 (0.62%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
genetic disorders			
subjects affected / exposed	0 / 308 (0.00%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	vitamin D	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 308 (0.00%)	0 / 322 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/3389415>