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High prevalence of severe vitamin D deficiency during the first trimester in pregnant women in Switzerland and its potential contributions to adverse outcomes in the pregnancy

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Summary

PURPOSE: Vitamin D is primarily known for its role in bone health. However, it has a much more diverse role in the human metabolism. Specifically, deficiency of vitamin D has recently been studied for its possible role in adverse pregnancy outcomes such as preeclampsia, gestational diabetes and preterm birth. Vitamin D levels largely depend on exposure to the sun and are influenced by nutritional habits at only a minimal level. In Switzerland, it is estimated that 40–50% of the population is vitamin D deficient. No specific data on pregnant women is available. The recommendations of the Swiss Federal Commission for Nutrition include a supplement of 600 IU of vitamin D to all pregnant women, despite the lack of data for this population in Switzerland. The primary aim of this study was to determine the prevalence of vitamin D deficiency among the population of pregnant women receiving prenatal care and giving birth at our clinic. We assumed that the prevalence of vitamin D deficiency in pregnant women in Switzerland is significantly higher than what has been estimated. Therefore, the current recommendations for vitamin D supplementation in pregnant women may be insufficient to achieve appropriate vitamin D levels. Furthermore, we aimed to address the issue of the potential influence of vitamin D deficiency on adverse pregnancy outcomes.

METHODS: We performed a retrospective, observational cross-sectional study of 1382 pregnant women attending prenatal care at our department between 2012 and 2015. Serum 25-dihydroxycholecalciferol (25(OH)D) levels were determined in the first trimester, and the patient's characteristics, the course of the pregnancy, any complications, the delivery and the neonatal outcome were analysed. The risk factors for vitamin D deficiency and its correlation with adverse pregnancy outcomes were assessed using a multivariate analysis.

RESULTS: The clear majority (73.23%) of the population studied were found to be vitamin D deficient, with serum levels of 25(OH)D <50 nmol/l. More importantly, severe vitamin D deficiency (25(OH)D levels below 25 nmol/l) was present in one third (34.2%) of all pregnant women. The mean 25(OH)D level was 36.72 ± 19.63 nmol/l. In the multivariate analysis, those with a high BMI and who belonged to ethnicities comprising people who are generally dark-skinned were found to be associated with lower 25(OH)D serum levels ($p < 0.0001$). We detected a seasonal influence: the mean 25(OH)D level was significantly higher during the summer season (April–September) compared to the winter season (October–March) ($p < 0.0001$). We found an association between low 25(OH)D serum level and gestational diabetes ($p = 0.0116$). Surprisingly, a low 25(OH)D level was also associated with decreased incidence of postpartum hemorrhage and placental retention ($p = 0.02$). We found no association between the 25(OH)D serum level and preeclampsia, preterm birth, postdate pregnancy, miscarriage, intrauterine growth restriction, bacterial vaginosis, mode of delivery, or neonatal birth weight and length.

CONCLUSION: We performed a retrospective analysis of serum 25(OH)D concentrations in pregnant Swiss women and found a mean serum 25(OH)D level of about 37 nmol/l and that one third of the overall study population had a serum 25(OH)D level below 25 nmol/l, and were thus seriously vitamin D deficient. Furthermore, the data demonstrate that vitamin D deficiency is associated with gestational diabetes. The current recommendations of vitamin D supplementation of 600 IU in pregnant women are therefore insufficient, and novel strategies, such as general screening for vitamin D deficiency, pre-conceptional timing of the supplementation and individually tailored dosing of vitamin D supplementation seem mandatory, potentially leading to improved maternal health and benefits to children's long-term health in Switzerland and worldwide. (trial registration ClinicalTrial.gov. Identifier: NCT02904720)

Keywords: *vitamin D, vitamin D deficiency, pregnancy, Switzerland, gestational diabetes, adverse pregnancy outcome*

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Introduction

Vitamin D is best known as a vitamin of the calcium and bone metabolism. More recently, vitamin D has been shown to have many other roles in human physiology. Indeed, vitamin D receptors are found in most of an organism's cells, including white blood cells, and may play a role in cell proliferation and differentiation and affect the immune system or insulin secretion and sensitivity [1]. Furthermore, recent reports indicate an association between low vitamin D levels and an increased risk of developing pregnancy complications such as disorders of placental implantation, pre-eclampsia, fetal growth retardation, gestational hypertension, impaired glucose tolerance and gestational diabetes, preterm birth, caesarean section, and other adverse conditions [2–5]. Recent studies report a higher incidence of postpartum depression in cases of vitamin D deficiency [6]. As a long-term consequence of vitamin D deficiency, women are at risk of developing severe osteoporosis [1]. A low vitamin D level in the mother can result in maternal hypocalcaemia, which in turn is a factor that promotes the development of neonatal seizures.

Negative effects of maternal vitamin D deficiency have also been reported in the newborn and for the offspring's development: long-term consequences for the child may range from rickets, increased susceptibility to respiratory illness, autoimmune diseases like Crohn's disease or diabetes mellitus type I, or even cancer, since vitamin D also has a modulatory action on the immune system [7–9]. Lower neonatal vitamin D status is related to autism spectrum disorder, and a link to developmental delay has recently been shown in the CHARGE case-control study [10].

There is emerging evidence that genetic and epigenetic factors may influence vitamin D status, and that the gene expression profiles of healthy pregnant women change during the course of pregnancy, suggesting that maternal vitamin D levels influence transcriptional profiles. These alterations of the maternal transcriptome may contribute to fetal immune imprinting and reduce allergic sensitisation in early life [11, 12]. New data suggest that there are indeed direct genomic alterations induced by the vitamin D administered during pregnancy that can alter birth outcomes [13–15].

Vitamin D is the only vitamin that can be synthesised by the body itself, with the help of ultraviolet B (UVB) irradiation. Nevertheless, vitamin D deficiency is quite common. In Switzerland, the prevalence of vitamin D deficiency has been shown to be 60% for the general population, with seasonal variability [16]. There is no published data on the prevalence of vitamin D deficiency in pregnant women in Switzerland.

There is no consensus among health experts on the optimal serum level of vitamin D to guarantee sufficient long-term bone mineralisation and to support the proper functioning of the whole organism. In the literature, most experts (IOM, WHO, NIH, EFSA) regard serum levels of 25(OH)D between 50 and 75 nmol/l as sufficient [17–21].

Treatment of vitamin D deficiency consists of consequent supplementation. There are several different supplementation protocols among different countries and health institutions [22]. Unfortunately, there is currently a lack of evidence concerning the best way to supplement vitamin D and the efficacy of vitamin D supplementation to improve pregnancy and neonatal outcomes. The current literature has clearly demonstrated that vitamin D supplementation is safe at up to 4000 IU/d, and to date, there are no reports of adverse events [4, 5, 21, 23–25].

The primary aim of this study was to determine the prevalence of vitamin D deficiency among the population of pregnant women receiving prenatal care and giving birth in our clinic. Furthermore, we aimed to assess baseline vitamin D levels, as well as the prevalence and degree of severity of vitamin D deficiency among the pregnant population receiving care at our clinic in Switzerland. We also aimed to compare our data to the existing data for the general population and to compare our results to the current Swiss guidelines, which recommend a routine supplementation of 600 IU of vitamin D to every pregnant women, without a prior assessment of their vitamin D levels. Prior assessment of vitamin D levels is only recommended if risk factors are present [16]. We further wanted to identify in our sub-population groups and confirm the known risk factors for vitamin D deficiency among pregnant women. We also wanted to study the influence of vitamin D on various pregnancy outcomes and to suggest how an optimised management strategy for vitamin D supplementation in pregnancy might look if our results are confirmed in further studies.

Materials and methods

Study stetting and design

In 2012, following the release of the Swiss guidelines on vitamin D deficiency by the Federal Commission for Nutrition, we started collecting the baseline vitamin D levels of pregnant subjects to rectify the lack of data on baseline vitamin D levels in pregnant women and the unknown prevalence of vitamin D deficiency in pregnant women in Switzerland.

We now intend to provide, for the first time, data on baseline vitamin D levels in pregnant women in Switzerland, and to explore possible associations of these levels with adverse pregnancy outcomes. This retrospective, observational cross-sectional study was performed at the Department of Obstetrics and Gynaecology of the University Hospital Bern in Switzerland.

The study was approved by the ethics committee of the University of Bern (Ref.-Nr. KEK-BE: 330/2015; Basec: 2015-00063) and was registered on ClinicalTrial.gov. (Identifier: NCT02904720).

Following the Swiss Federal Act on research involving human beings (Human Research Act, HRA) of 30 September 2011 (Status as of 1 January 2014), Art. 33–35, written informed consent for further use of non-genetic health-related personal data is not necessary.

Patient recruitment and selection

All pregnant women who had their serum vitamin D levels measured during the first or second trimester of their pregnancy and who took prenatal care and had their deliveries at our institution between 2012 and 2015 were included. Vitamin D levels were routinely checked at the first antenatal visit by women taking prenatal care at our clinic. All

data were retrieved retrospectively from the patients` electronic files.

Vitamin D supplementation and current Swiss guideline recommendation

In our antenatal clinic, we recommend maternal multivitamin supplementation with Elevit® Pronatal, Bayer, containing 500 IU of vitamin D, to every patient. Additional vitamin D is added according to their individual vitamin D needs. The pregnant subjects were reviewed every 5–6 weeks and their history of adherence was taken. Compliance was reported to be usually quite good. The costs of vitamin D testing and supplementation were covered by the Swiss health insurance system.

In our clinic, supplementation of at least 1000 IU/d was administered orally throughout the pregnancy in cases of deficiency. Women with adequate vitamin D levels were routinely supplemented with 600 IU/d orally, following the Swiss Federal Commission for Nutrition's recommendations [16]. A follow-up measurement of the vitamin D level was not routinely performed, as it was assumed that vitamin D levels were adequately restored after the course of the treatment.

Analytical method

Using blood samples obtained from a standard venipuncture at admission, a quantitative laboratory analysis of 25-hydroxycholecalciferol (25(OH)D), the precursor form of bioactive vitamin D, was performed in our Center of Laboratory Medicine, Inselspital, University Hospital Bern using chemiluminescent immunoassays (CLIA) on a Liaison XL (Diasorin).

For 25(OH)D, total internal quality control was performed using the LIAISON by Diasorin 25 OH vitamin D total control set (REF 310601), level 1 and 2 in each series, as well as after calibration. The external quality control was done by round robin tests four times a year by the Swiss Centre for Quality Control.

For our study, we established that a sufficient 25(OH)D level was indicated by a value >50 nmol/l. A mild deficiency was present when values were between 25–49 nmol/l, and a severe deficiency was present if levels were below 25 nmol/l [17–20].

Data acquisition

We retrospectively reviewed the electronic files of the 1382 selected patients. Relevant data such as body mass index (BMI), origin, season of testing, smoking status, pregnancy outcomes including the occurrence of complications (see below), mode of birth and gestational age at birth, and the neonatal outcomes of birth weight and length were extracted and anonymised.

Variables

The adverse pregnancy variables added to the multivariate analysis were selected after reviewing the relevant literature, especially existing reviews and meta-analyses [24, 26–32]. The most frequently studied maternal and fetal adverse outcomes were selected.

Preeclampsia was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg at two separate times (at least 4 hours apart) in a previously normotensive patient, whether or not associated with the presence of a proteinuria ≥300 mg/24h.

Gestational diabetes mellitus (GDM) was defined following the WHO 2013 criteria (fasting plasma glucose ≥5.1 mmol/l, 1h plasma glucose ≥10 mmol/l, or 2h plasma glucose ≥ 8.5 mmol/l after a standard 75g oral glucose tolerance test performed around the 28th week of gestation).

Postpartum haemorrhage (PPH) was diagnosed in all vaginal deliveries with a blood loss ≥500 ml.

Placental retention was diagnosed when the placenta had not undergone expulsion within 30 minutes after the delivery.

Preterm birth was defined as a delivery which took place before completing the 37th week of gestation.

Postdate pregnancy was defined as a delivery which took place after the 40th week of gestation.

Miscarriage was defined as a clinically recognised pregnancy loss before the 20th week of gestation or as the extraction of an embryo or fetus weighing ≤500 g, following the WHO criteria.

Intrauterine growth restriction (IUGR) was diagnosed when a fetus failed to achieve its growth potential, in the case of progressive deviation from its growth curve or in the case of SGA (fetus with weight <10th percentile) combined with signs of placental insufficiency such as oligohydramnios or abnormal umbilical artery Doppler.

Bacterial vaginosis was diagnosed in the case of clinical symptoms of colpitis associated with a positive vaginal smear test or following the Amsel criteria.

The mode of delivery was classified as vaginal birth or caesarean section.

Statistical analysis

The primary endpoint, the prevalence of vitamin D deficiency, was analysed with an empirical estimation of the proportion of interest and with a score-type confidence interval.

To identify the risk factors (BMI, ethnicity, religion, smoking status, season at testing) for the numerical primary outcome, a linear regression model was performed. The linear regression analysis was performed by modelling the numerical outcome of vitamin D status. As this was log-normally rather than normally distributed, a log transformation was applied to the outcome.

A backward selection modelling method was chosen because there were many potential risk factors for vitamin D deficiency. Two-way interactions were also considered in order not to miss any important effects. No adjustments were made for potential factors due to the retrospective nature of this study.

A correlation analysis was performed because associations between several perinatal outcomes and the primary outcome were of interest. These outcomes could not be included in the regression model since they could not be seen as predictors of vitamin D status.

For the analysis associations between the numerical primary endpoint and several outcomes, measurements of associations were computed. Numerical outcomes (weight, length and gestational age at birth) were analysed with Pearson's correlation coefficient.

For the analysis of categorical outcomes (preeclampsia, gestational diabetes, abortion, postpartum haemorrhage, etc.), the numerical primary endpoint was split into two categories describing whether a value was regarded as deficient or not. Following this, odds ratios (ORs) in the case of a dichotomous variable and chi-square tests in the case of a nominally scaled variable were performed.

For all association measures, a confidence interval (CI) and a p-value for the null of no association were also computed. No correction for multiple testing was applied due to the explorative nature of this retrospective observational study. The level of significance was set to 0.05.

All calculations for the statistical analysis were done with R, version 3.2.2. (The R Project for Statistical Computing, Vienna, Austria).

Results

Out of the 1382 women who had vitamin D testing at our clinic, 229 were lost to follow-up. For the assessment of the prevalence of vitamin D deficiency among pregnant Swiss women, all 1382 women who had their vitamin D levels tested were included.

For the second part of this study, which analysed the associations between vitamin D levels and adverse pregnancy outcomes, only the 1153 women for whom we conducted a complete follow-up until the delivery at our clinic were included. The baseline characteristics of the population studied are presented in figure 1 and table 1.

Prevalence of vitamin D deficiency

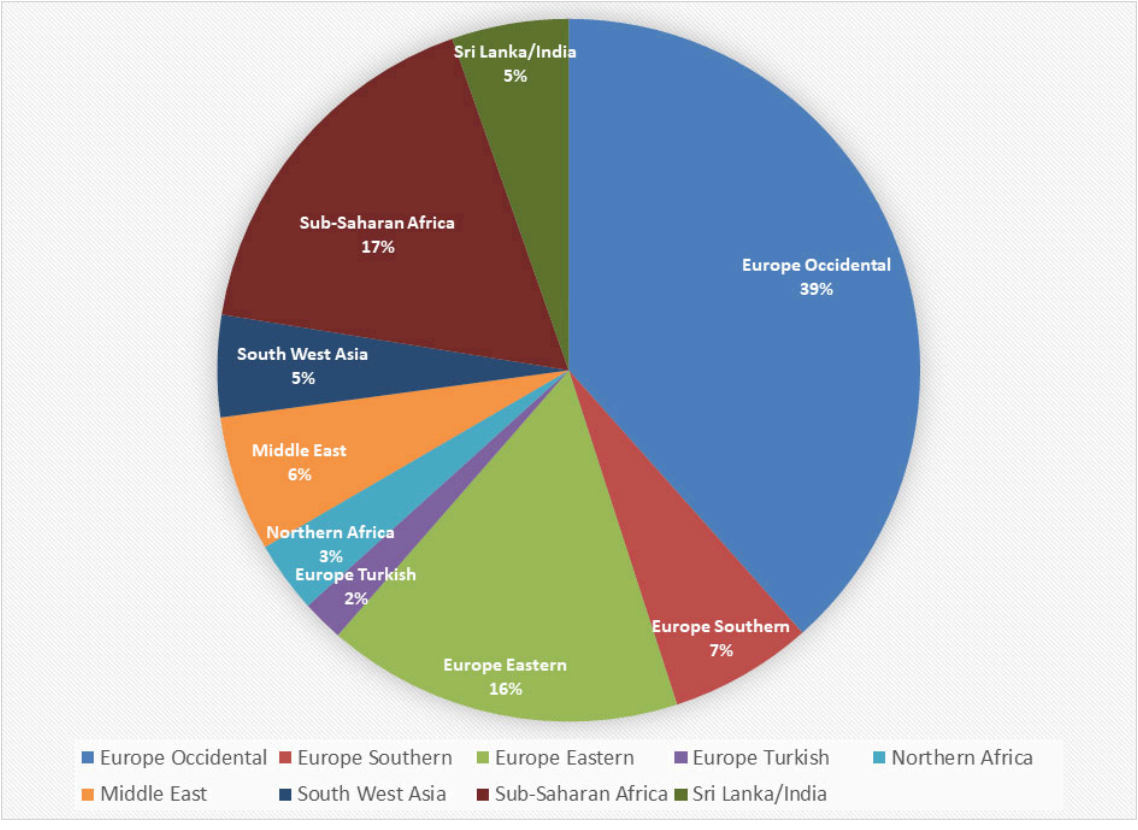
Among the 1382 women who had their 25(OH)D serum level tested, only 26.77% had a sufficient vitamin D level (≥50 nmol/l). Mild deficiency, defined as 25(OH)D levels between 25 and 50 nmol/l, was present in 38.93%, while severe deficiency, defined as 25(OH)D levels below 25 nmol/l, was present in 34.2% of all the women tested, which gives an overall rate of vitamin D deficiency (25(OH)D < 50 nmol/l) of 73.23%. These results are presented in table 2.

The mean 25(OH)D serum level was 36.72 nmol/l (SD 19.6).

Table 1: Baseline characteristics of the population studied.

Patients with 25(OH)D testing		1382
Testing period from April to September (%)		677 (48.99)
Testing period from October to March (%)		705 (51.01)
Patients with 25(OH)D testing and follow-up until birth		1153
Median maternal age at testing (years)		30 (IQR 22–38)
Median gestational age at testing (weeks)		12 (IQR 8–16)
Median BMI (kg/m^2)		23 (IQR 16–30)
Smoking mothers (%)		70 (6.17)
Ethnic origin (%)	European:	730 (63.31)
	- Occidental	- 443 (38.42)
	- Southern	- 76 (6.59)
	- Eastern	- 189 (16.39)
	- Turkish	- 22 (1.91)
	Northern Africa	38 (3.30)
	Middle East	72 (6.24)
	South West Asia	54 (4.68)
	Sub-Saharan Africa	197 (17.09)
	Sri Lanka/India	62 (5.38)

Figure 1: Distribution of the population studied according to their ethnic origin.



Risk factors for vitamin D deficiency during pregnancy

Known risk factors for vitamin D deficiency were confirmed by our findings and are presented in table 3.

Patients who had blood samples taken during the period from October to March were more likely to have a vitamin D deficiency than those who were tested between April and September (p <0.0001). Patients with higher BMI values were significantly more likely to suffer from vitamin D deficiency (p <0.0001). Smoking was not found to be a risk factor for vitamin D deficiency (p = 0.0924).

The statistical analysis demonstrated that subjects of European descent (including western + eastern + southern Europe and Turkey) and those from North Africa, the Middle East and Asia, i.e., people with lighter skin, are significantly less likely to show a vitamin D deficiency compared to Africans or Sri Lankans/Indians (p <0.0001), i.e., people with darker skin living in Switzerland. The results for the various ethnic groups are summarised in figures 2 and 3.

Table 2: Distribution of vitamin D status among the 1382 patients with vitamin D testing (total = 1382).

Sufficiency (%)	370 (26.77)
Mild deficiency (%)	538 (38.93)
Severe deficiency (%)	474 (34.30)
Mean serum level of 25(OH)D (nmol/l)	36.72 (SD 19.6)

Associations between vitamin D status and pregnancy outcomes

A statistically significant association with vitamin D deficiency was found only for the development of gestational diabetes (p = 0.0116; OR = 0.5932, 95%CI 0.3872–0.8826). Postpartum haemorrhage and placental retention, which can be regrouped under "abnormalities of third stage of labour", were found to be less likely in patients with a lower vitamin D status (p = 0.0188 and p = 0.0277).

No significant association could be observed between the vitamin D status and the occurrence of:

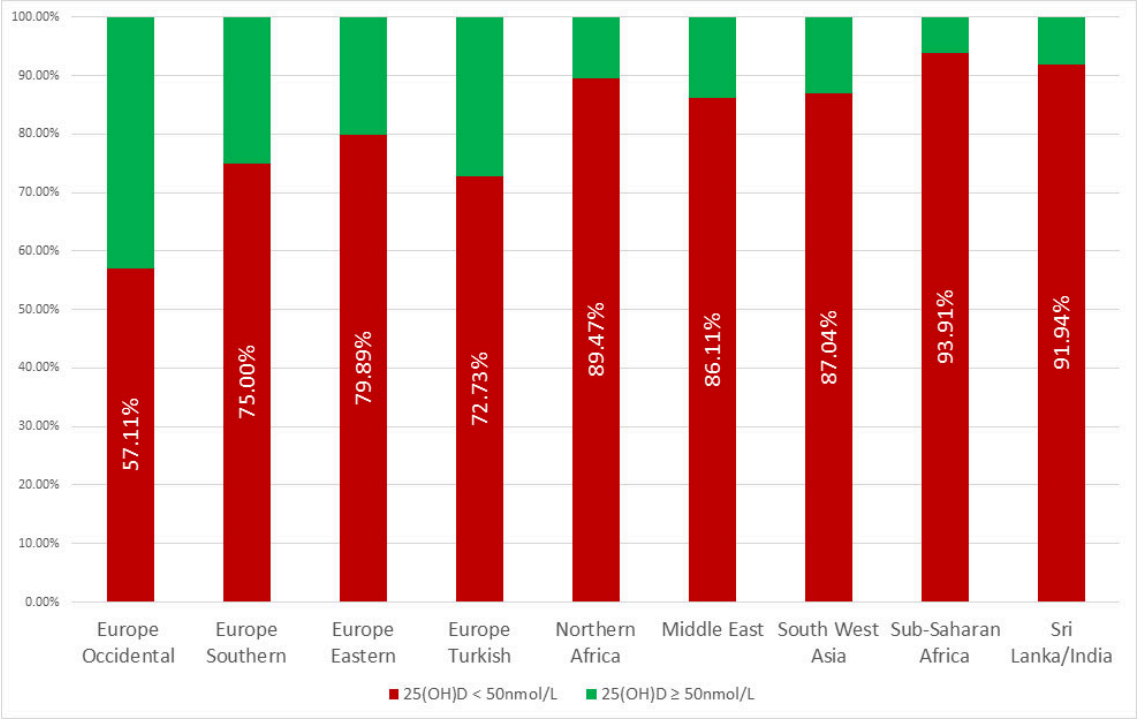
- bacterial vaginosis (p = 0.4420)
- pregnancy hypertension and/or preeclampsia (p = 0.1606)
- small-for-gestational-age newborn or intrauterine growth retardation (p = 0.3695)
- prematurity (p = 0.3154)
- early miscarriage (p = 0.0892)
- caesarean delivery (p = 0.1992)

Table 3: Linear model for vitamin D status and risk factors*.

Variable	Estimate	Std error	t value	p-value
(Intercept)	3.8366	0.125895	30.4750	<0.0001
Ethnicity	0.6418	0.0372	17.2320	<0.0001
BMI	−0.0220	0.0035	−6.2870	<0.0001
Smoking	−0.0045	0.0615	−0.0730	0.9419
Season at testing	−0.1950	0.0349	−5.5880	<0.0001
Gestational age at testing	0.0047	0.0030	1.5850	0.1133

* The modelled outcome was the numerical vitamin D status

Figure 2: Vitamin D status among the various ethnic origins.



Interestingly, gestational age at birth was closely negatively correlated with vitamin D level (correlation coefficient −0.0978, 95%CI −0.1498 to −0.0453; p = 0.0003). This means that low vitamin D levels were not associated with preterm births, but on the contrary, the lower the vitamin D level, the higher the gestational age at birth. No significant correlations were found concerning newborn weight (p = 0.2006) or length (p = 0.5808).

The results concerning the associations between low vitamin D levels and pregnancy outcomes/complications are presented in tables 4 and 5.

Discussion

Summary of results

Our study is the first large cross-sectional cohort study of 25(OH)D level measurements in pregnant women in Switzerland, showing that three quarters of them are vitamin D deficient and over one third are severely vitamin D deficient. This corresponds to our primary hypothesis that pregnant women have a much higher prevalence of severe vitamin D deficiency compared to the rate for the general population in Switzerland stated in the Swiss Federal Commission for Nutrition report [16]. This finding has consequences for vitamin D supplementation recommendations

Figure 3: Mean value of 25(OH)D according to the various ethnic origins.

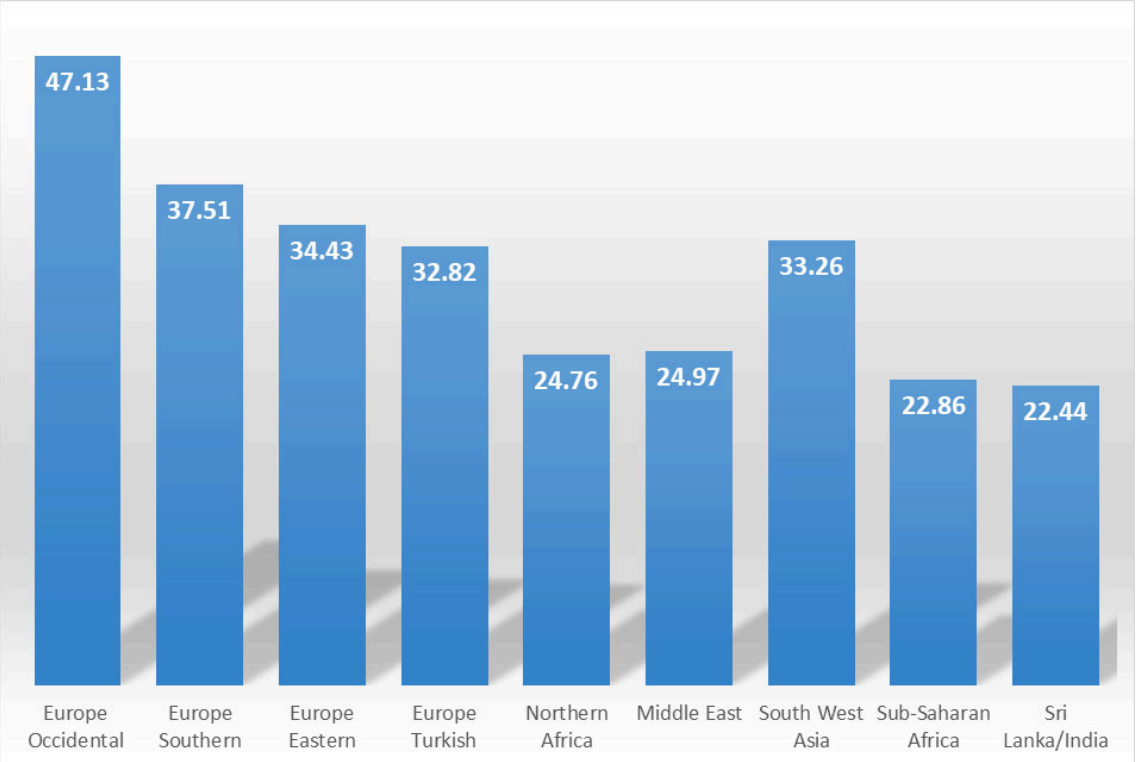


Table 4: Associations between vitamin D status and pregnancy outcomes.

Outcome	n (%)	% with vitamin D deficiency	Mean vitamin D (nmol/l)	SD	OR	95% confidence interval	p-value
Gestational diabetes	167 (14.5)	81.44	36.31	19.59	0.5932	0.3872–0.8826	0.0116
Bacterial vaginosis	36 (3.1)	77.78	40.62	19.41	0.6912	0.2730–1.5181	0.4420
Preeclampsia	24 (2.1)	87.50	33.46	19.37	0.4042	0.0914–1.1900	0.1606
SGA/IUGR	109 (9.5)	77.06	38.05	19.45	0.7961	0.4911–1.2473	0.3695
Prematurity	85 (7.4)	68.24	41.63	19.70	1.2769	0.7855–2.0322	0.3154
Miscarriage	46 (4)	84.78	36.56	19.54	0.5050	0.2030–1.0768	0.0892
Delivery by caesarean section	388 (33.7)	75.52	39.12	19.65	1.1968	0.9154–1.5744	0.1992
Prolonged pregnancy	129 (153)	74.42 (74.51)	41.99 (27.29)	19.64	0.9292	0.6056–1.3930	0.7558
Placental retention	46 (4)	58.70	46.73	19.39	1.9841	1.0709–3.6044	0.0277
Postpartum haemorrhage	90 (7.8)	62.22	46.34	19.60	1.7349	1.1023–2.6935	0.0188

IUGR = intrauterine growth restriction; OR = odds ratio; SD = standard deviation; SGA = small for gestational age

Table 5: Associations for numerical outcomes.

Outcome	Mean value	Standard deviation	Correlation coefficient	Confidence interval	p-value
Weight of neonate at birth	3337.3g	1148.16	0.0434	−0.0231 to 0.1095	0.2006
Length of neonate at birth	49.3cm	2.83	−0.0189	−0.0858 to 0.0482	0.5808
Gestational age at birth	39th 2/7	2.35	−0.0978	−0.1498 to −0.0453	0.0003

in Switzerland. Currently, supplementation of 600 IU is recommended for all pregnant and breastfeeding women. For women with a severe vitamin D deficiency, supplementation of 1500–2000 IU is recommended, as stated in the Swiss Federal Commission guidelines. However, general serum measurements are not currently recommended.

The effect of the supplementation of 600 IU vitamin D on 25(OH)D levels can be estimated using the dose–response calculations proposed by Heaney. The administration of 400 IU is expected to increase 25(OH)D concentrations by about 10.0 nmol/l [33]. This means that even if 800 IU vitamin D were to be supplemented to all pregnant women, over a third would not reach the recommended minimum threshold level of 50 nmol/l. There are recent publications of RCTs highlighting the fact that a 600 IU daily supplement is insufficient to prevent vitamin D deficiency, and that higher dosing of vitamin D is required to establish sufficiency [4, 21, 23].

Comparison with published research

The current literature contains conflicting evidence regarding the association between vitamin deficiency and adverse pregnancy outcomes. A recent Cochrane review of 30 randomised and quasi-randomised trials concluded that supplementing pregnant women with vitamin D alone probably reduces the risk of preeclampsia, gestational diabetes and low birthweight, and may reduce the risk of severe postpartum haemorrhage [34]. However, additional rigorous, high-quality and larger randomised trials are required to evaluate the effects of vitamin D supplementation in pregnancy, particularly in relation to the risk of maternal adverse events. This is in accordance with the conclusions of many other studies and meta-analyses, with a wide heterogeneity of populations studied and applied methodologies for both vitamin D substitution and assessment, on the relationship between maternal vitamin D status and pregnancy outcomes [35–37].

Measurement of vitamin D

In line with general clinical practice, we measured only total 25(OH)D. However, there are recent data indicating that free 25(OH)D might be superior to routine total 25(OH)D as a characteristic of vitamin D status in pregnancy [38].

Risk factors for vitamin D deficiency

Our findings regarding the prevalence of vitamin D deficiency are in line with several published studies from all over the world. One of them, conducted in northern Italy, observed a prevalence of vitamin D deficiency of 70.6% [39]. In a 2018 study from Saudi Arabia, the prevalence was as high as 82.5% [40]. A Chinese study obtained almost the same result, with a prevalence of 82.6% [6]. On the contrary, a recently published Australian study reported a much lower percentage of pregnant women with a vitamin D deficiency, but that difference can be easily explained by differences in sun exposure [41]. We found two recently published Swiss studies that reported slightly lower prevalences of vitamin D deficiency. The first one included 204 patients and focused on differences in the rates of vitamin D deficiency detected in pregnant women depending on their skin color. It found that overall, 63% of these women were vitamin D deficient [42]. The second study included 305 patients and obtained a prevalence of vitamin D deficiency of 53.4% [43].

Our study confirms most of the risk factors for vitamin D deficiency reported in the literature (winter season, BMI, ethnic groups with darker skin, smoking status). Indeed, our results show the presence of a significant seasonal variability of vitamin D status. We also found an inverse relationship between vitamin D status and BMI, which is explained by a smaller skin surface area for vitamin D synthesis in comparison to the total body volume [44]. Our results do not confirm smoking as a risk factor for vitamin D [45]. Like several others [39, 42, 46–48], our study confirms that populations from Southeast Asia and Africa have a significantly higher risk of vitamin D deficiency than the occidental population. This difference between the various ethnic groups has been explained in the literature: it is due to the degree of skin pigmentation, which influences the ability of the body to absorb sunlight for the synthesis of vitamin D [1]. This is of increasing interest in view of current global migration patterns.

Negative pregnancy outcomes

Gestational diabetes mellitus

Like numerous others, our study confirms the association between low vitamin D levels and the occurrence of gestational diabetes mellitus (GDM) [40, 41, 46, 49]. An Australian study from 2014 [46] reported a seven-fold increase in the likelihood of developing GDM if the women were vitamin D deficient during the early stages of pregnancy. Another Australian study, published in 2018, observed a 53% decreased risk for gestational diabetes mellitus in women with high (> 81 nmol/l) "standardised" vitamin D status when compared to moderate to high (63−81 nmol/l) [41]. In a multiethnic cohort of 745 pregnant women from Norway, a higher proportion of women from ethnic minorities had GDM ($p < 0.01$) and low 25(OH)D levels ($p < 0.01$), compared to European women. However, after adjustments for confounding factors, in particular ethnicity, vitamin D deficiency was not associated with GDM [50].

A meta-analysis from 2014, based on 20 observational studies and regrouping up to 9200 patients, also indicated a consistent association between vitamin D deficiency and an increased risk of GDM [51]. A meta-analysis of 29 observational studies conducted in 2018, which included 28,982 participants of whom 4634 were diagnosed with gestational diabetes, showed that maternal vitamin D insufficiency was associated with a significant increase in the risk of gestational diabetes of 39% (pooled OR 1.39, 95%CI 1.20−1.60), with moderate heterogeneity (I^2 50.2%; $p = 0.001$) [52].

Another meta-analysis of 26 studies found that vitamin D deficiency among mothers in general may be related to an increased risk of gestational diabetes (OR 1.18, 95%CI 1.01−1.35; $p < 0.001$). Subgroup analysis showed that the results concerning this association may vary with study design but do not change with country of origin [53].

Gestational diabetes is strongly associated with an adverse pregnancy outcome, as well as with long-term adverse effects on the offspring, which likely occur due to epigenetic modifications of the fetal genome (fetal programming), which is exposed to altered conditions in diabetic moth-

ers. The impact of gestational diabetes in pregnancy and on the offspring's future shows a need to find efficient prevention and intervention strategies. A question that should be raised is whether vitamin D supplementation is helpful in preventing the development of gestational diabetes, a condition that develops in about 2–5% of all pregnant women and has become considerably more common during the last decade [54].

To our knowledge, three recently published double-blind RCTs presented positive data regarding the effect of vitamin D supplementation on GDM. Vitamin D supplementation during the first and second trimesters of pregnancy was effective in reducing GDM and controlling the glucose tolerance test [55]. A high dose of vitamin D supplementation (50,000 IU every 2 weeks) significantly improved insulin resistance in pregnant women with GDM [56], and supplementation among pregnant women with GDM resulted in a decrease in the occurrence of maternal polyhydramnios and infant hyperbilirubinemia compared with a placebo [57].

Postpartum haemorrhage and placental retention

Surprisingly, our results show a significant inverse relationship between vitamin D status and the occurrence of both postpartum haemorrhage and placental retention. We do not have an explanation for this finding and very few existing publications address this subject. A case-control study found that women with uterine atony had a significantly lower mean of vitamin D concentration than those without uterine atony, which could be explained by the fact that low vitamin D can result in muscle weakness. Another study [46] did not find any such association.

Preeclampsia

Similar to our study, there have been observational studies [46, 47] which showed negative results for any association between vitamin D levels and preeclampsia. A meta-analysis of 12 studies from 2014 [58] suggested that low maternal serum 25(OH)D concentrations increase the risk of preeclampsia and that vitamin D supplementation lowers this risk. However, the quality of evidence was insufficient to determine a causal association. Another study [59], based on data from up to 700 patients who developed preeclampsia, concluded that vitamin D deficiency may be a risk factor for severe preeclampsia, but that it is not associated with preeclampsia overall or its mild subtypes. A recently updated meta-analysis of 23 studies found that vitamin D deficiency (25(OH)D <20 ng/ml = <50 nmol/l) was significantly associated with a risk of preeclampsia (fixed $p < 0.0001$; random $p = 0.0029$; fixed OR = 1.33; random OR = 1.54) and that this association can be specific up to 90% at a 10.60 ng/ml cut-off [60]. The findings on the relationship between vitamin D deficiency and preeclampsia in the literature are therefore inconclusive, possibly because, according to Hollis and Wagner, supplementation should occur prior to placentation [21].

Low birth weight/SGA

Yet again, in agreement with our study, there are published results showing a lack of any significant association between vitamin D and SGA and/or low birth weight. However, many observational studies [3, 61] have shown that women with lower vitamin D levels are more likely to give birth to SGA fetuses, and pregnant women who deliver SGA fetuses have lower vitamin D levels. This has been explained by the action of vitamin D on bone formation and the known fact that birth weight is directly correlated with skeletal growth.

Our results did not demonstrate any association between vitamin D status and the occurrence of bacterial vaginosis, pregnancy losses or prematurity.

Several observational studies [3, 51] have found that women with a lower vitamin D status have a higher risk of bacterial vaginosis. The underlying mechanism is possibly related to the role that calcitriol plays in the immune system. By reducing susceptibility to infections, vitamin D could also be a protective factor against the premature rupture of the membranes and prevent prematurity.

Few studies concerning the connection between vitamin D and prematurity are available. We found only one study with significant results, a retrospective case–control study [62] which concluded that vitamin D levels were significantly lower in women who delivered at preterm compared to in those who delivered at full term.

As an immune modulator, vitamin D also plays a role in maternal immunosuppression, without which the fetus could not survive. Therefore, vitamin D deficiency has been implicated as a risk factor for recurrent pregnancy losses. There is limited data available concerning this last outcome. However, a recent study from Denmark reported that concentrations of 25(OH)D <50 nmol/l were associated with a greater than two-fold increase in the adjusted hazard ratio for first-semester miscarriage [63]. A recent review of the literature on recurrent pregnancy loss included 11 studies which reported a high prevalence of vitamin D insufficiency/deficiency in women with recurrent pregnancy loss and suggested that this could be associated with immunological dysregulation and consequently with recurrent pregnancy loss. However, there is currently no evidence concerning the benefits of supplementation on this outcome [64].

Mode of delivery

Few studies have assessed the mode of delivery. However, most of those that have are similar to ours in the sense that they did not demonstrate any significant association between vitamin D and delivery by caesarean section [3, 46, 65]. In a cross-sectional study by Merewood et al. in 2009 [66], delivery by caesarean section was almost four times more common in women with vitamin D levels < 37.5 nmol/l compared to those with levels over 80 nmol/l. Similar to the ideas around uterine atony, the theory is that low vitamin D can result in muscle weakness and negatively affect the stages of labour.

Strengths of the study

This study is one of the first large studies presenting data on the vitamin D status of pregnant women in the first trimester in Switzerland. The data highlight the magnitude of the problem and raise awareness of this global health issue. Our data also show that vitamin D deficiency is not a problem restricted to developing countries, but also affects pregnant women in developed countries.

These data also contribute to establishing a possible link between vitamin D deficiency and gestational diabetes mellitus.

This study has two further major strengths. The first is the large number of included subjects. The second is that the study population was not a selective cohort of typical Swiss women, but a longitudinal sample of the overall population living in a modern Swiss city, which is much more representative of the daily practice.

Limitations and weaknesses of the study

Limitations of this analysis result firstly from the retrospective nature of the study and the difficulty in recalling past events. This may contribute to possible biases in the study.

As we only included the most frequently studied adverse maternal and fetal outcomes after a narrative review of the literature, less frequent adverse events like hypercalcemia of newborns were not included.

There are several parameters, like dietary and lifestyle habits, sunshine exposure and clothing preferences, which would have been of interest. However, we were unable to obtain the data to allow us to include them in the analysis.

It would have also been quite interesting to incorporate the follow-up results of the vitamin D levels from the second and third trimesters. However, no results were available for this population as we assumed that vitamin D levels would, by then, have returned to the normal range. Nevertheless, we now recognise that it would have been of value to check the vitamin D levels. Therefore, we have subsequently introduced a follow-up check of vitamin D levels in the second trimester.

Due to the retrospective nature of the study, no structured data on the vitamin D supplementation could be provided. The pregnant subjects were reviewed every 5–6 weeks and the history of adherence was taken, with compliance good overall.

Low levels of vitamin D appear to be associated with both positive and negative outcomes. Therefore, the resulting available evidence needs to be interpreted with caution. However, it remains unclear whether this association is causal, owing to the observational design of the study.

We are aware that our findings must be interpreted with caution and that further research is needed to provide more evidence on this topic and to promote a change in the guidelines.

Despite the many important health benefits of vitamin D, there is controversy regarding the definition of vitamin D deficiency and what the vitamin D requirement should be. In addition, critical windows of exposure to adequate vitamin D levels during fetal maturation remain to be defined [67].

Conclusion

Our study shows a high prevalence of severe vitamin D deficiency in pregnant women. Furthermore, the data suggest that vitamin D deficiency is linked to gestational diabetes.

In our opinion, the current recommendations of vitamin D supplementation of 600 IU in pregnant women are insufficient to establish an adequate vitamin D level. Novel strategies such as general 25(OH)D measurement in pregnancy and adjusted supplementation of vitamin D should be evaluated in further studies, potentially leading to improved maternal health and benefits to children's long-term health in Switzerland and worldwide. Pre-conception supplementation of vitamin D, as is recommended for folic acid, may even be considered as part of a novel approach, so that women begin their pregnancy with already sufficient levels of vitamin D, especially as there are no negative effects to be expected from starting supplementation earlier.

Further well-designed studies are required to assess the efficacy of targeted, 25(OH)D level-adjusted vitamin D supplementation during pregnancy on vitamin D levels in newborns and, finally, on clinical outcomes. This is of utmost importance, as ensuring a sufficient supply of vitamin D in both the mother and the child has great potential for the prevention of birth complications and significantly affects the health of the child throughout his/her life.

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Potential competing interests

The authors have no conflicts of interest to declare.

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