

# Neonatal Risks of Vitamin D and Iodine Supplementations during Pregnancy

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## Abstract

**Background:** The consumption of dietary supplements (DS) has increased by almost 10% last decade. This trend may be true also for pregnant women; however, it was reported that pregnant women do not sufficient and correct knowledge on nutritional needs during pregnancy. Thus, we here attempted to determine the French situation of how French pregnant women take DS and its social-clinical significance using questionnaires, with special reference to vitamin D (VD) overtaking. **Materials and Methods:** A prospective multi-centric study was performed in three maternities in Paris. One hundred-fifty questionnaires were administered to pregnant women by midwife. **Results:** Thirty-four patients were interviewed at the maternity ward of the Deaconesses, 61 at the Pitié-Salpêtrière and 55 at Armand Trousseau. During pregnancy, DS started mainly during the first trimester. Frequently, doctors initially prescribe them and women tended to continue to take them thereafter. Possible VD overdosage was observed. **Conclusion:** We here characterized French pregnant women in terms of DS during pregnancy and also, to our knowledge, for the first time emphasized the risk of vitamin D overdose during pregnancy in France. However, since the cumulative dose throughout the pregnancy was not determined here, definite conclusion of whether women really take overdose of this supplement may not be made. Women of higher socio-professional society tended to consume more DS during pregnancy, and, thus, further monitoring may be needed especially to this fraction of pregnant women.

## Keywords

Dietary Supplement (DS), Pregnancy, Hypercalcemia, Vitamin D (VD), Iodine

## 1. Introduction

In less than a decade, the consumption of food supplements has increased by almost 10% [1] [2]. Dietary supplements of pregnancy have been implicated in cases of hypercalcemia and neonatal hypothyroidism [3]. In pregnant women, as well as in the general population, energy intakes are recommended as: 55% of carbohydrates, 30% - 35% of lipids and 10% - 15% of proteins [4] [5]. Folic acid needs to be supplemented in the pre-conception period and until the end of the first trimester and in vitamin D at the 6th [5] [6]. No supplementation is needed for other vitamins [4] [7]. Knowledge needs to be emphasized in pregnant women about nutritional needs during pregnancy [8]. Taking medication during pregnancy can affect the fetus so pregnant women need to ask a health professional (midwife, doctor, pharmacist) before taking any pills or drugs [9] [10].

The dietary supplement (DS) is defined by Decree No. 2006-352 of 20 March 2006 [11]. Nutrient deficiencies are rare in the general population except for vitamin D, where nearly 50% of the general populations are in deficit [12] [13]. The midwives, doctors and pharmacists should be aware of the risk of neonatal hypercalcemia after vitamin D supplementation during pregnancy [14]-[19].

National College of Gynecologists-Obstetricians (CNGOF) in 1997 and the National Agency for Sanitary Safety, Food, Environment, Work (ANSES) have recommended to monitor the DS in their real conditions of use and identifies adverse effects [20] [21]. They study the consumption of DS since 1998 and during the period 2006-2007 that shown 20% of adults have consumed (DS), twice in women (26.5%) than in men (12.6%). Consumers generally have a high level of education. At the national level, there is higher consumption in the South and East 22% against 18% in the North and West. The motivation for the purchase is mainly due to the prescription or advice from a health professional (58%), the place of purchase is mainly in pharmacy (54%) and rarely on the internet (1%). The main expectations of consumers are: "fight against fatigue" (33%), "solve a health problem" (21%), "stay healthy/fight against diseases" (17%). Among women, 6% of consumers say they consume it to meet the needs related to pregnancy. Finally, "balancing one's current diet" and "supplementing insufficient dietary intake" only account for 3% and 2% of motivations. The study shows that DS intake is influenced by the seasons, more important in winter than during the summer [1].

In June 2017, the INCA 3 study is published. It was conducted over the 2014-2015 period. Compared to the previous study, there is an increase in DS consumption (from 20% to 29%). The main place of purchase is still the pharmacy (45%) but the purchase by internet has grown strongly from 1% to 11%. Women, people with a high level of education and seasonality are consistent characteristics in DS consumption. We know that the main consumers are 18 to 44 years old [2].

The selling price of the DS is not regulated. His purchase therefore represents

a certain budget. This is why the studies found on the subject are on populations from favored countries. A study conducted in the United States, Germany, Sweden and Finland shows that pregnancy DS consumption is associated in all countries with primiparity; on the other hand, women under 25 years old are less likely to be users. Some factors such as high level of education are found in the United States and Sweden but not in Finland and Germany. Tobacco use is associated with lower turnover in the Nordic countries, the United States and Germany, but this factor is not significant. In Finland, alcohol consumption during pregnancy and pathological first-trimester markers are related to an increase in DS consumption. This can be explained by a probable representation of the DS which differs according to the countries. In Finland, where consumption is increased in the event of a “pejorative” event for pregnancy (pathological serum markers, tobacco consumption) the DS would be represented as a remedy that could combat these derogatory events. In Sweden and Germany, overweight people (body mass index (BMI) > 25 kg/m<sup>2</sup>) tend to use less DS. Finally, in the United States, where ethnicity studies are permitted, there is no link with pregnancy DS consumption [22].

A study conducted in Saudi Arabia shows that the use of pregnancy DS was very high (71.5%). Factors such as education level, household income, having 1 or 2 children are associated with DS consumption. BMI, professional activities do not affect consumption. 81.6% of respondents believe that supplementation is important and that neonatal outcomes are better and the study shows that there is no association. Consumers take a majority of DS following the advice of their doctor (65.7%) [23].

We have seen that many pregnancy DS consumption factors and DS more generally are common as the socioeconomic level. Some parameters were found to be consumption factors in some countries but not in others (tobacco). Now we will see the situation in France. A cohort study conducted in 2013, showed that the use of dietary supplements of pregnancy in France was increased if these factors were present: primiparity (relative risk (RR): 2 to 3), to have high incomes (>3130 €/month) (RR: 2.09), live in the Paris region (RR 2 to 4 according to other French regions), be from a higher socio-professional category (RR: 2 by contribution to the unemployed). On the other hand, age, marital status, level of education, knowledge of PNNS recommendations and consumption of organically produced foods are not significantly related to pregnancy DS consumption. Use of DS during pregnancy follows a prescription or recommendation by a physician in 86.7% of cases [24].

In February 2007, the French Agency for Sanitary Safety of Foods (AFSSA), published recommendations (RDAs) for folic acid and vitamin D and for claims claimed by a dietary supplement as intended for pregnant women. The opinion states that vitamin B9 intake should not be continued beyond the first trimester of pregnancy, which is in line with the recommendations in force. Regarding the vitamin D intake, the intake of 400 IU/day (10 µg/day) is in agreement with the

recommendations. Iodine contributions must be found in the foods rich in iodine (milk and dairy products, crustaceans, eggs, enriched salt...) and that only the patients at high risk (geographical area deficiency, smoking...) are likely to have drug supplementation throughout the pregnancy. For iron, the AFSSA recalls that women must be supplemented in cases of iron deficiency anemia and systematic supplementation is not justified, and that the ideal to prevent anemia is to have a varied diet and balanced. Finally, the AFSSA says that these DS are not adapted to the nutritional needs of all pregnant women without distinction and adds that the information leaflets should draw attention to the risks of simulation induced by the DS and other enriched foods and the consumption of several products was discouraged [25].

In May 2017, ANSES described 84 cases reports about DS adverse reactions during pregnancy [3]. Eighteen were imputable. The adverse effects are mainly hypercalcemia and neonatal hypothyroidism. 2 cases were strongly imputable, eleven cases of possible accountability, and five cases of questionable accountability. ANSES confirmed that 5 cases of neonatal hypercalcemia and 2 cases of neonatal hypothyroidism where DS would be involved. In reported cases, DS were not the only source of vitamin D or iodine. ANSES informed pregnant women to be advised by a health professional on the use of DS during pregnancy.

## 2. Material & Method

The study focused on the population of patients giving birth in the 12th and 13th districts of Paris. Indeed, there are maternities of different types, public and private of collective interest.

The expected number of patients surveyed is at least 134 in total, to have significant results.

The distribution of the workforce varies according to the type of maternity. That is 23% of patients interviewed in type 1, 40% in type 2 and 37% in type 3, as observed in the 2016 national perinatal survey [26]. All patients were asked about their living conditions and the course of their pregnancy, including the recommended supplements. Patients who consumed DS had additional questions about their use of these products, their use during this pregnancy.

The inclusion criteria were French language comprehension, she had to have given birth for at least 24 hours. The criteria for non-inclusion were that the patient was in the service of the diaper suites but had not given birth (patient being tripped); patients who cannot communicate orally in French (foreign patients who do not speak French, hearing-impaired patients who cannot communicate otherwise than by sign language).

Studied variables were: age, gestity, parity, BMI, geographical origin/nationality, socio-professional category and marital status. These data are compared to the 2016 national perinatal survey to find out to what extent the model of this population can be generalized to the French population. The profile of consumers

were: socio-professional category, marital status, type of housing, eating habits, diet, physical activity, consumption of alcohol and other drugs, geographic origin/nationality, age, BMI, presence of chronic disease. The variables which could affect the intake of dietary supplements were: the professional following the pregnancy in the first 6 months, a pregnancy spontaneously obtained, the type of pregnancy, the discovery of a pathology during pregnancy, taking vitamin D in the 6th month and peri-conceptional folic acid, performing prenatal and parenting preparation (PNP) and early prenatal care (EPP). The variables which could affect the dietary supplements consumption during pregnancy, use outside pregnancy, consumption, the beginning of the consumption of the DS, an interruption of the taking of these, and the reason for stopping, the average time of use if it was interrupted, the reason for taking the DS and the place of purchase.

Student's T test was used when the values used were averages and Chi-square tests when the values found are ratios. The Student test was performed with the software included in Excel®. For Chi 2 tests, calculations were performed with the Open-Épi® software. The alpha risk was set at 0.05 and the confidence intervals are at 95%.

### 3. Results

The study was conducted from November 16, 2018 to January 23, 2019. The total number of patients that could be included in the study was 150. The questionnaire was distributed in 3 maternity homes in the East of Paris: The Deaconesses (type 1), La Pitié-Salpêtrière (type 2), and Armand Trousseau (type 3). Thirty-four patients were interviewed at the maternity ward of the Deaconesses, 61 at the Pitié-Salpêtrière and 55 at Armand Trousseau.

Pregnancy supplements were found to start mainly during the first trimester ( $p < 0.000001$ ). Following a medical prescription ( $p = 0.0001$ ) and the prescriber was usually a gynecologist-obstetrician ( $p = 0.000008$ ) with a prescription ( $p < 0.0000001$ ). Other prescribers were general practitioners, midwives and nutritionists.

DS was mainly advised by a pharmacist ( $p = 0.014$ ).

Finally, in patients who consumed dietary supplements until the end of pregnancy, 2 started in the second trimester and 3 during the third trimester. In these patients, all had taken the recommended dose of vitamin D, so the 2 patients who started in the second trimester may be considered at risk for vitamin D overdose.

### 4. Discussion

This is, to our knowledge, the first report on the risk of vitamin D overdose during pregnancy in France Regarding the risk of vitamin D overdose; this is the first study to address this risk.

As a first step, we will see if the surveyed population corresponds to the model

of patients having a pregnancy in France, then we will see if the profile of the consumers of dietary supplements of pregnancy is different from that of the consumers of the general population. Finally, we will see if our study finds the same characteristics in consumers than in the National Perinatal Survey 2016 [26].

The proportion of patients of French origin is lower in this population than at national level (48% vs. 81.4%) and the same is true for French nationality (79.3% vs. 85.9%) (Table 1). This can be explained by the fact that historically, the Paris basin is a place of arrival of different waves of immigration. Regarding the marital status of patients, there is a much larger share of married patients compared to the French population (52% vs. 42.2%). In contrast, there is a smaller share of PACS (14.7% vs 41.3). In the 2016 Perinatal Survey, marital patients were not included and were included in the single category. However, when we look at the percentage of couples “not living in a couple” which corresponds to the share of singles, the percentage is 5.2% which is similar to the 4.7% observed in this study.

For the socio-professional categories, there is a very large share of senior managers and intellectual professions (32.7% vs. 13.3%). This is explained by the fact that Paris is an economic engine of France and that many large companies are headquartered in Paris or La Défense, the business district. Given the location of the study, as well as the specificity of the Paris region, it seems difficult to expand the results obtained at a national level (Table 2).

**Table 1.** Population baseline.

	Population	Diaconesses Hospital	p	Pitié Hospital	p	Trousseau Hospital	p
n	150	34		61		55	
Age	32.1 [31.8 - 32.8]	33.9 [32.4 - 35.3]	<b>0.03</b>	30.3 [29.6 - 31.3]	<b>0.003</b>	33.1 [31.9 - 34.2]	0.166
Gestivity	2.1 [1.9 - 2.3]	2.2 [1.7 - 2.7]	0.702	1.9 [1.7 - 2.2]	0.283	2.2 [1.9 - 2.6]	0.525
Parity	1.7 [1.6 - 1.8]	1.7 [1.3 - 2.0]	0.956	1.7 [1.4 - 1.9]	0.917	1.7 [1.5 - 1.9]	0.868
BMI	23.8 [23.0 - 24.8]	22.8 [21.7 - 23.9]	0.146	24.5 [23.1 - 25.9]	0.392	23.6 [22.5 - 24.8]	0.821
Patients	72/150 (48%)	23/34	<b>0.04</b>	22/61	0.117	27/55	0.891
French nationality	119/150 (79.3%)	32/34	<b>0.03</b>	45/61	0.385	42/55	0.643
<b>Marital status</b>							
Married	78/150 (52%)	20/34	0.480	30/61	0.7133	28/55	0.891
Single	7/150 (4.7%)	0	0.233	5/61	0.3379	2/55	0.801
PACS	22/150 (14.7%)	5/34	0.966	8/61	0.7902	9/55	0.754
Marital life	43/150 (28.7%)	9/34	0.815	18/61	0.8966	16/55	0.945
<b>Socio-professional categories</b>							
Liberal activities	7/150 (4.7%)	2/34	0.739	3/61	0.911	2/55	0.801

**Table 2.** Dietary supplement status.

	DS users	Non users	p
n	59	91	
French origin	31/59	41/91	0.376
French nationality	50/59	69/91	0.194
<b>Marital status</b>			
Married	32/59	46/91	0.861
Single	1/59	6/91	0.189
PACS	10/59	0/91	<b>0.00005</b>
Marital life	16/59	27/91	0.744
<b>Socio-Professional category</b>			
Liberal activities	2/59	5/91	0.593
Third sector activities	23/59	26/91	<b>0.03</b>
Intermediate profession	18/59	25/91	0.690
Employee	12/59	25/91	0.331
No professional activity	4/59	10/91	0.4083
Professional activity during pregnancy	47/59	67/91	0.408
<b>Habitation status</b>			
Personal habitation	58/59	84/91	0.123
Relatives	0	5/91	0.079
Hostel	1/59	2/91	0.879
<b>Food status</b>			
Food variety and equilibre	49/59	82/91	0.219
Junk-food	7/59	4/91	0.105
Pesco-vegan	1/59	1/91	0.787
Vegan	2/59	4/91	0.797

Higher socio-professional category consumed more DS than general population. Prescription was the main motivation for taking DS [24].

This study showed that follow-up by a gynecologist-obstetrician was associated with an increase in DS intake, contrary to pregnancies followed by midwives in maternity where patients do not consume dietary supplements. It should be noted that in the literature no study has been done on the practice of prescriptions by midwives and in particular on the prescription of vitamins during pregnancy.

The literature is not unanimous on certain criteria that may influence the consumption of DS such as smoking, marital status. No smoking status before pregnancy and PACS were associated with an increase in DS intake.

In this study, a very small proportion (2/59) of patients were aware of a potential risk of overdose. Although the patients are not very aware of this risk, we will specifically study the case of folic acid (vitamin B9), vitamin D and iodine. Folic acid: Scientific authorities recommend peri-conception vitamin B9 supple-



mentation to prevent neural tube closure abnormalities. This supplementation can be provided by food by increasing the consumption of folate-rich foods such as green vegetables and if not, a supplementation of 100 to 200 µg/day can be made. Vitamin B9, in patients without consuming food supplements, a third (27/91) had not received folic acid peri-conception or during the first trimester after pregnancy known. Some begin their consumption during the peri-conception period. A large proportion of these women also took folic acid in the first trimester (32/45). The recommendations are that the intake should be 200 µg per-conceptional. Patients take 4 times the dose because the majority of food supplements on the market are dosed at 400 µg and practitioners also prescribe 400 µg of folic acid since no drug is dosed at 200 µg. In addition, for people with an antecedent neural tube closure abnormality it is recommended to supplement them with 5 mg/day of folic acid 1 month before the beginning of pregnancy and up to 2 months of pregnancy. These doses are well above the 800 µg/d that can be taken by patients taking dietary supplements and the folic acid that has been prescribed (**Table 3**). Finally, from a metabolic point of view, vitamin B9 is a water-soluble vitamin and in the case of high consumption, it is eliminated mainly in faeces and in a smaller quantity in the urine [19]. Thus the amounts of folic acid absorbed and circulating are quite low.

The recommended vitamin D intake during pregnancy was the single dose of a 100,000 IU ampoule at the beginning of the 7th month. Or daily intake of 400 IU from the beginning of pregnancy or 1000 IU/day at the beginning of the third quarter, but these types of patterns are more restrictive [20]. In non-consuming patients, almost three-quarters (70/91) of them had the recommended vitamin D supplementation.

As previously stated, overdosed patient with vitamin D was defined with pregnancy supplements for the duration of her pregnancy and having received a vitamin D ampoule dosed at 100,000 IU at the beginning of the 7th month or at another time of pregnancy. In this study, this proportion represents more than 3/4 of the patients. Thus, it was important to be vigilant to a possible over consumption of vitamin D with DS. ANSES reports 5 cases of neonatal hypercalcaemia where the implication of dietary supplements of pregnancy is doubtful or possible. These cases could be treated by stopping the administration of vitamin D in the newborn. Indeed, according to the current pediatric recommendations, infants should receive up to 18 months of 800 to 1200 IU of vitamin D per day [6]. We can thus understand that if we take every day of her pregnancy a dose of vitamin D, it was stored in the adipose tissue mainly constituted during the first part of the pregnancy and therefore that the day of the taking of 100,000 IU prescribed, the patient is quickly overdosed. Vitamin D contained in pregnancy food supplements has been implicated in cases of overdose [27] [28] [29] [30].

ANSES, in its May 2017 report, recalls that there have been two cases of congenital hypothyroidism where the involvement of dietary supplements is possible. Thus, since this alert was issued, all notices were updated.



**Table 3.** Comparison pregnancy status and dietary supplementation.

	<b>DS users</b>	<b>Non users</b>	<b>p</b>
n	59	91	
Age (mean)	32.6 [31.0 - 34.2]	31.8 [30.9 - 32.7]	0.246
Primiparity	32/59	48/91	0.861
Multipare	27/59	43/91	0.861
BMI (mean)	24.3 [23.0 - 25.6]	23.5 [11.5 - 13.5]	0.316
Tobacco (non users)	51/59	65/91	<b>0.032</b>
Alcohol (non users)	54/59	87/91	0.3321
Weight gain during pregnancy	12.5 [10.8 - 14.2]	12.5 [11.5 - 13.5]	0.902
No Sport practice during pregnancy	27/59	45/91	0.664
Sport practice during pregnancy	20/59	27/91	0.589
No chronical diseases	45/59	74/91	0.463
No infertility	54/59	81/91	0.638
Pregnancy plan	57/59	80/91	0.066
Single pregnancy	57/59	90/91	0.400
<b>Professional status</b>			
Physician	1/59	6/91	0.189
Gyneco-obstetrician	48/59	56/91	<b>0.010</b>
Private activity	35/59	40/91	0.069
In maternity ward	13/59	16/91	0.506
Mide-wife	10/59	27/91	0.079
Private activity	5/59	6/91	0.672
In maternity ward	5/59	21/91	<b>0.020</b>
PMI	0/59	2/91	0.366
<b>Gestational diabetes</b>			
Yes	9/59	20/91	0.319
Regime	3/59	8/91	0.423
With insuline	6/59	12/91	0.598
Without insuline	50/59	71/91	0.319
Other diseases during pregnancy	46/59	73/91	0.734
PNP activity	40/59	50/91	0.121
EPP activity	21/59	23/91	0.183
<b>Dietary supplement (DS)</b>			
Vitamin D during pregnancy	47/59	70/91	0.517
Folic acid supplement during the first trimester during pregnancy	42/59	64/91	0.916
During peri conceptus	20/59	22/91	0.204
After pregnancy beginning	22/59	42/91	0.290
No folic acid supplementation	17/59	27/91	0.916

This study was able to show that the profile of women who consume pregnancy supplements was similar to the general population of these consumers. The proportion of these people is around 40% in the study population. DS consumption was made mainly during the first trimester and part of this population continues throughout the pregnancy. These food supplements were overwhelmingly prescribed by gynecologists-obstetricians and purchased in pharmacies. A relatively small number of patients were aware of the risk of overdose [28]. Recommendations need to be updated with new vegan and vegetarian habits during pregnancy.

## 5. Conclusion

This is, to our knowledge, the first report on the risk of vitamin D overdose during pregnancy in France. However, since the cumulative dose throughout the pregnancy was not determined here, definite conclusion of whether women really take overdose of this supplement may not be made. Women of higher socio-professional society tended to consume more DS during pregnancy, and thus further monitoring may be needed especially to this fraction of women.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## **Glossary**

AFSSA: French Agency for Sanitary Safety of Foods

AJR: Recommended Daily Contributions

ANSES: National Agency of Sanitary Security, Food, Environment, Work

DS: Dietary Supplement

CNGOF: French National College of Gynecologists-Obstetricians

CSP: Public Health Code

EPP: Early Prenatal Interview

BMI: Body Mass Index

INCA: National Individualized Study of Food Consumption

PNNS: National Health Nutrition Plan

PNP: Preparation for Birth and Parenthood

QCM: Multiple Choice Questionnaire