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Araştırma/Research

Does the deficiency of 25-hydroxy vitamin D effect the placental peptides (free β-human chorionic gonadotropin and pregnancy-associated plasma protein A) levels?

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Abstract

Objective

In this study, we analysed that low maternal 25 hydroxy vitamin D (25(OH)D) levels cause an increase in the level of 1,25 dihydroxy vitamin D in the syncytiotrophoblasts by placental hydroxilation and also we analysed the effects of low syncystiotrofoblastic stimulation on placental peptides (free β-human chorionic gonadotropin and pregnancy-associated plasma protein A) secretion..

Material and Methods

This retrospective study was included 225 pregnant women at 11-14 weeks of gestation attending the outpatient clinic of our hospital for first trimester screening test from January 2017 to December 2017. Vitamin D levels were deficient in 145 pregnant women and adequate in 80 pregnant women. Serum 25(OH)D concentrations were measured at 11–14 weeks gestation in 225 singleton pregnancies using liquid chromatography-tandem mass spectrometry in the same labaratory.

We assessed the relationship between vitamin D, free β-human chorionic gonadotropin (free β-hCG) and pregnancy associated plasma protein A (PAPP-A) levels during pregnancy.

Results: There was a negative correlation between PAPP-A levels and maternal age at sampling (p=0.219). There was a positive correlation between free β-hCG levels and maternal age at sampling (p=0.034). There was a negative correlation between Low 25(OH)D levels and free β-hCG levels (p=0.071). There was a positive correlation between Low 25(OH)D levels and PAPP-A levels (p=0.414).

Conclusion

There was no statistically significant relationship between free β-hCG, PAPP-A levels and vitamin D in the first trimester.

Key words: Vitamin D, PAPP-A, free β-hCG, screening test,

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Maternal 25 hidroksi D Vitamini eksikliği plasental peptidlerin (Serbest β-hCG ve PAPP-A) düzeyini etkiler mi?

ÖZET

Amaç: Biz bu çalışmamızda 25 hidroksi vitamin D düzeyi düşük gebelerde, sinsisyotrofoblastlarda plasental hidroksilasyonla yeterince 1,25 dihidroksi vitamin D sentezi gerçekleşmezse bunun sonucu olarak sinsisyotrofoblastik uyarı eksik yapılarak plasental peptidler olan serbest β-hCG ve PAPP-A'nın sekresyonu azalabilir mi sorusuna cevap aramaktayız.

Gereç ve Yöntemler: Bu retrospektif çalışmamıza Medikal Park Göztepe Hastanesi'ne Ocak -Aralık 2017 yılı içerisinde başvuran 11-14. Gebelik haftasında ikili tarama testi yapılmış 225 gebe dahil edilmiştir. Çalışma retrospektif gözlemsel arşiv taraması ve tek merkezli olarak planlanmıştır. Arşiv dosya taraması için Medikal Park Göztepe Hastane kompleksinden (2017/13007 sayılı) akademik kurum onay kararı alınmıştır.

İkili tarama testindeki PAPP-A ve serbest β-hCG seviyeleri ile ilk trimesterde aile sağlığı merkezlerinde rutin bakılmış olan 25 hidroksi D vitamini düzeyleri arasındaki olabilecek istatistiksel ilişkiyi araştırdık. Vitamin D düzeyi normal olan 80 gebe ile vitamin D düzeyi eksik olan 145 gebenin ikili test sonuçları karşılaştırılmıştır.

Çalışmamıza IVF (in vitro fertilizasyon) gebeliği olanlar, ikiz gebelikler, sigara içenler, gastrointestinal sistem ve tiroid beziyle ilgili herhangi bir hastalığı olanlar, pregestasyonel diyabet tanısı olanlar, sistemik hastalığı ve inflamatuar barsak hastalığı (Ülseratif kolit, Crohn, vb) olanlar, gastrit şikayetleri olanlar, D vitamini desteği alan gebeler alınmamıştır.

Bulgular: PAPP-A seviyeleri ve anne yaşı arasında negatif korelasyon saptandı (p=0.219). Serbest β-hCG seviyesi ile anne yaşı arasında pozitif korelasyon bulundu (p=0.034). Düşük 25(OH)D vitamini seviyeleri ile serbest β-hCG arasında negatif korelasyon saptandı (p=0.071). Düşük 25(OH)D vitamini ile PAPP-A seviyeleri arasında pozitif korelasyon saptandı (p=0.414) .

Sonuç: İlk trimesterde serbest β-hCG, PAPP-A seviyeleri ile vitamin D arasında ilişki istatistiksel olarak anlamlı bulunmamıştır.

Anahtar kelimeler: D vitamini, PAPP-A, serbest β-hCG, ikili tarama testi

INTRODUCTION

Vitamin D is crucial pleiotropic secosteroid hormone for health and avoiding disease. The vitamin D receptor, wich connects the active form of vitamin D [1,25(OH)2D] to induce both transcriptional and non-genomic responses, mediates vitamin D activitions. The widely known functions of D vitamin are calcium uptake and on bone metabolism, but more new studies emphasize the importance of unusual influences of vitamin D in various cell types (1–4).

Recent studies have highlighted the significance of nonclassical acts of vitamin D in pregnancy and the placenta. Vitamin D, which labors as a modulator of inoculation, cytokine production and immune response to infections, is produced by the placenta.There have defined the metabolism and the cellular responses of vitamin D in some study. And it has abtracted the act of placental trophoblast in pregnancy and the fetus (5, 6).

In addition, the human placenta has the enzymatic activity of 1-alpha-hydroxylase (CYP27B1) and 24-hydroxylase (CYP24A1), which are included in vitamin D synthesis and metabolism (7).

However, some studies put forward vitamin D can induce estrogen, progesterone, and beta human chorionic gonadotropin (β-hCG) synthesis (7, 8). Whereas another study suggests that it inhibits cytokine secretion (9).

MATERIAL AND METHODS

This retrospective study was approved by the Ethics Committee of Göztepe Medicalpark Hospital, Istanbul, Turkey (2017/13007). A total of 225 pregnant women were included in this study from January 2017 to December 2017. We assessed the relation among 25(OH)D, free β-hCG, and PAPP-A levels during pregnancy. All participants have been living in Istanbul.

Individuals with gastrointestinal disorders, thyroid disorders, pregestational diabetes, and inflammatory bowel disease and those who had undergone IVF pregnancy or were smokers were not included in this study.

At 11^{th} and the $13^{th} \pm 6$ weeks of gestation the maternal age, gestational age at blood sampling,

body mass index (BMI), and vitamin D levels of the women in this study were recorded.

As patients *were classified according* to their serum *levels* of *25(OH)D as follows:* sufficient (≥30 ng/ml), n = 80; insufficient (10–30 ng/ml), n = 97; and deficient (<10 ng/ml), n = 33.

Only 35.5% of the study subjects had sufficient serum 25(OH)D levels, whereas 43.1% and 21.3% of these patients were found to have insufficient and deficient levels, respectively.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) software package version 17.0 for Windows. The Shapiro-Wilk test was utilised to shown the normality of data distribution. Spearman rho coefficients were calculated to detect correlations between age, gestational week, BMI, 25(OH)D, PAPP-A, and B-hCG levels. Statistical significance was evaluated p value of <0.05.

RESULTS

The study population characteristics are shown in Table 1**.** PAPP-A and 25(OH)D levels were negatively correlated with maternal age at sampling (p = 0.219 and p = 0.234, respectively), whereas free β-hCG levels positive correlated with it (p = 0.034). PAPP-A levels and 25(OH)D levels showed a positive correlation with gestational age (p = 0.281 and p = 0.021, respectively), whereas free β-hCG levels showed a negative correlation with gestational age (p = 0.032). Negative correlations were found between BMI and PAPP-A levels (p = 0.051) as well as BMİ and free β-hCG levels (p = 0.065), whereas a positive correlation was found between BMİ and 25(OH)D levels (p = 0.021).

Table 1. Basal characteristics and 25 (OH) D, Free β-hCG, PAPP-A status of the studied population (n=225)

Parameters	**Free β-hCG levels (IU/L)median±std.dev**	**PAPP-A levels(IU/L) median±std.dev**	**25(OH)Dlevels(ng/ml) median±std.dev**
All (n=225)	*37.90±29.56*	3.60±4.44	24±12.79
Age <30 (n= 131) ≥30 (n= 94)	 37.90±32.29 38.83±13.09 p = 0.034	 3.78±4.21 3.40±4,77 p= 0.129	 26.30±12,34 21.55±13,07 p= 0.234
Body mass index(kg/m2) <25(n= 138) 25-30 (n= 77) ≥30 (n= 10)	 38,41±10.80 38.60±33.18 32.06±31.41 p= 0.065	 3.59±4,66 3.69±4.18 1.69±2,70 p= 0.051	 24.20±13.00 23.60±12.87 24.10±9.56 p=0.021
Gestasyonel age at entry <12 weeks(n=144) ≥12 weeks (n= 61)	 36.40±25,73 38.98±9.62 p=0.032	 2.91±4,71 3.76±4.35 p=0.281	 22.00±11.58 25.20±13.11 p=0.203

*: p value for the intragroup comparison as determined with the Shapiro-Wilk test.

Table 2 showed that there was a negative correlation between low 25(OH)D levels and free β-hCG levels ($p = 0.071$), while there was a positive correlation between low 25(OH)D levels and PAPP-A levels ($p = 0.414$).

Free β-hCG and PAPP-A levels were significantly correlated with each other ($p < 0.001$), but neither of them correlated with 25(OH)D levels.

Table 2. Free β-hCG and PAPP-A levels and correlations with 25(OH)D status.

Parameters	Free β-hCG levels (IU/L)median±std.deviation	PAPP-A levels(IU/L) median±std.deviation
Deficient Low 25 (OH) D (n= 48)/%21.3	46.72±31,03 p=0.071	3.27±2,51 p=0.032
İnsufficient25 (OH) D (10-30 ng/ml) (n =97)/%43.1	38.60±28.10 p=0.001	2.88±1,65 p=0.001
Sufficient 25 (OH) D (n=80)/%35.5	36.38±14.19 p=0.001	8.02±5.42 p=0.001

Deficient = (< 10 ng/ml); İnsufficient (10-30 ng/ml)Sufficient = (≥30 ng/ml).
*: p value for the intragroup comparison as determined with the Shapiro-Wilk test.

DISCUSSION

Nowadays, one of two maternal serum markers in utilized for screening between the 11th and 14th gestational weeks is PAPP-A. The placental syncytiotrophoblast and decidua basalis have produced it. PAPP-A raises the bioavailability of the insulin-like growth factor, which intervenes trophoblast input and modulates glucose and amino acid transport in the placenta (10-13). Reduced levels of PAPP-A are established in participation with an abnormal placental function which has composed the basis for the first-trimester screening of fetal Down's syndrome (14-17).

The main role of free β-hCG is to protect the corpus luteum as well as progesterone secretion during the first trimester of pregnancy, and it is produced by the systiotrophoblast(10-12).Despite, its metabolic significance, the vitamin D attends also endocrine system in distinct reproduction-related processes in both females and males, such as the maintenance of sperm quality, implantation, cell proliferation, placental hormone/cytokine secretionocal and immune response (18-20). During pregnancy vitamin D deficiency is also associated with several obstetrical complications (21).

Although the criteria for defining enough serum vitamin D level still remain controversial, a study indicates that at least 30 ng/ml of vitamin D is required in serum to maintain an optimal health condition (22).

1,25 (OH) $_2$D and CYP27B1 play a role in autocrine and paracrine immunomodulator networks, which are prominent during pregnancy (23). 1,25(OH)2D influences macrophages and decidual dendritic cells, which in turn interact in the maternal–fetal interface to induce T-regulatory cells (24). Further, trophoblasts insulated from the placenta of preeclamptic cases have only one-tenth of the CYP27B1 enzyme activity in trophoblasts in non complicated pregnant women (25). Though it is unclear the role of vitamin D in pre-eclampsia (26), there is a hypothesis, which is low vitamin D levels disrupt the normal Th1–Th2 cytokine stability, with higher Th1 cytokine expression adversely affecting the immunological tolerance to embryo implantation (27).

The present review article suggests vitamin D role in pregnancy from a trophoblast perspective, with special importans on the potential role of 1,25(OH)2D as a regulator of trophoblast invasion to maintain optimal levels of placental peptides during early pregnancy.

CONCLUSION

Placental peptides levels of first-trimester do not accommodate with vitamin D levels, suggesting a non-placental 25(OH)D production. Obviously, further studies relating vitamin D influance will subcribe to recovery in maternal health.

Ethics Committee Approval: Ethics committee approval for this study was received from Göztepe Medical Park Hospital/Istanbult ethics Commitee.

Informed Consent: None, due to the retrospective study**.**

Conflict interest: None. (The authors declared no conflict interest)

Financial Disclosure: None.

REFERENCES

1. Özkan B, Döneray H. The non-skeletal effects of vitamin D. Çocuk Sağlığı ve Hastalıkları Dergisi 2011;53:99-119.

2. Perez-Lopez FR. Vitamin D: the secosteroid hormone and human reproduction. Gynecol Endocrinol 2007;23:13–24.

3. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357: 266–81.

4. Lucas RM, Ponsonby AL, Pasco JA, Morley R. Future health implications of prenatal and early-life vitamin D status. Nutr Rev 2008;66:710–20.

5. Evans KN, Bulmer JN, Kilby MD, Hewison M. Vitamin Dand placental-decidual function. J Soc Gynecol Investig 2004;11:263–71.

6. Evans KN, Nguyen L, Chan J, Innes BA, Bulmer JN, Kilby MD, Hewison M. Effects of 25-OHvitamin D3 and 1,25-dihydroxy vitamin D3 on cytokine production by human decidual cells. Biol Reprod 2006;75:816–22.

7. Avila E, Dı´az L, Barrera D, Halhali A, Me´ndez I, Gonza´lez L, et al. Regulation of vitamin D hydroksilases gene expression by 1,25- dihydroxy vitamin D3 and cyclic AMP in cultured human syncytiotrophoblasts. J Steroid Biochem Mol Biol 2007;103:90–6.

8. Barrera D, Avila E, Herna´ndez G, Me´ndez I, Gonza´lez L, Halhali A, et al. Calcitriol affects hCG gene transcription in cultured human syncytiotrophoblasts. Reprod Biol Endocrinol 2008;6:3.

9. Guibourdenche J, Frendo JL, Pidoux G, Bertin G, Luton D, Muller F, et al. Expression of pregnancy-associated plasma protein-A (PAPP-A) during human villous trophoblast differentiation in vitro. Placenta 2003;24(5):532-9.

10. Pe´rez-Lo´pez FR, Can˜ as E, L'Hermite M, Lo´pez E,Roncero MC, Robyn C. Prolactin and human chorionic gonadotrophin (HCG) in amniotic fluid during the two last trimesters of pregnancy. Int Res Commun 1974;2:1101–02.

11. Pujol-Amat P, Gamissans O, Cabero L, Pe´rez-Lo´pez FR, Benito E, Calaf J, et al. Effects of synthetic luteinizing hormone-releasing hormone on serum gonadotrophins, prolactin and chorionic somatomammotrophin during the last trimester of pregnancy.. Springer Verlag 1975; 246–49.

12. Pe´rez-Lo´pez FR, Tierz JA, Abo´ s MD, Pellejero S, Teijeiro J.Dopaminergic regulation of human prolactin, ACTH, aldosterone,TSH, placental lactogen, chorionic gonadotropin and estriol during pregnancy. Akademiai Kiado 1982; 459–66.

13. Bersinger NA, Keller PJ, Naiem A, Fischer M, Schneider H. Pregnancy-specific and pregnancy-associated proteins in threatened abortion. Gynecol Endocrinol 1987;1:379–84.

14. Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH, et al. First-trimester maternal serum PAPP-A and serbest-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol 2004;191:1446–51.

15. Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. Screening for trisomy 21 by maternal age, fetal nuchal translucency thickness, serbest β-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 2008;31:618–24.

16. Bayes-Genis A, Conover CA, Overgaard MT, Bailey KR, Christiansen M, Holmes DR Jr,et al. Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. N Engl JMed 2001;345: 1022–29.

17. Krantz DA, Larsen JW, Buchanan PD, Macri JN. First trimester Down syndrome screening: serbest b-human chorionic gonadotropin and pregnancy-associated plasma protein A. Am J Obstet Gynecol 1996;174:612–16.

18. Ramlau-Hansen CH, Moeller UK, Bonde JP, Olsen J, Thulstrup AM. Are serum levels of vitamin D associated with semen quality? Results from a cross-sectional study in young healthy men. Fertil Steril 2011;95:1000–04.

19. Shin JS, Choi MY, Longtine MS, Nelson DM. Vitamin D effects on pregnancy and the placenta. Placenta 2010;31: 1027–34.

20. Equils O, Hewison M. A role for vitamin D in placental immunology. J Infect Dis 2010;201:1950–51.

21. Lewis S, Lucas RM, Halliday J, Ponsonby AL. Vitamin D deficiency and pregnancy: from preconception to birth. Mol Nutr Food Res 2010;54:1092–102.

22. Pérez-López FR, Fernández-Alonso AM, Ferrando-Marco P, González-Salmerón MD, Dionis-Sánchez EC, Fiol-Ruiz G, et al. First trimester serum 25-hydroxyvitamin D status and factors related to lower levels in gravids living in the Spanish Mediterranean coast. Reprod Sci 2011;18:730–36.

23. Christakos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ. Vitamin D: metabolism. Endocrinol Metab Clin North Am 2010;39:243–53.

24. Zehnder D, Evans KN, Kilby MD, Bulmer JN, Innes BA, Stewart PM, et al. The ontogeny of 25-hydroxyvitamin D3 1alpha-hydroxylase expression in human placenta and decidua. Am J Pathol. 2002;161:105–14.

25. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting Edge: Vitamin D mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol. 2007;179:2060–3.

26. Halhali A, Tovar AR, Torres N, Bourges H, Garabedian M, Larrea F. Preeclampsia is associated with low circulating levels of insulin-like growth factor I and 1,25-dihydroxyvitamin D in maternal and umbilical cord compartments. J Clin Endocrinol Metab. 2000;85:1828–33

27. Hyppönen E. Vitamin D for the prevention of preeclampsia? A hypothesis. Nutr Rev. 2005;63:225–32.