ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

A STUDY OF MATERNAL AGE AND THYROID STATUS AND ITS ASSOCIATION WITH NEONATAL CONGENITAL HYPOTHYROIDISM

Dr. Balaji.K. [1], Dr. Sukanya Mukherjee [2*]

[1]Associate Professor , Department of Biochemistry, DM Wayanad Institute of Medical Sciences, Naseera Nagar, Meppadi, Wayanad district – 673 577, Kerala – India.

[2]Associate Professor, Department of Obstetrics & Gynaecology , DM Wayanad Institute of Medical Sciences, Naseera Nagar, Meppadi, Wayanad district – 673 577, Kerala – India.

[*]Corresponding Author

ABSTRACT

The prevalence of congenital hypothyroidism is high in India at 5.7 per 10,000 infants and an incidence rate of 1 in 244 in Kerala state. Neonatal mass screening programs have been largely successful in early diagnosis of congenital hypothyroidism. Both, very young and advanced maternal age are considered at risk for adverse pregnancy outcomes which in turn may be a factor for development of congenital hypothyroidism in neonates. The studies related to the role of maternal age as a risk factor for development of congenital hypothyroidism are minimal. Not much studies are available which analyse the association of adequately treated maternal hypothyroidism on the neonatal thyroid dysgenesis and other causes of neonatal congenital hypothyroidism. The study collected data about the age and thyroid status of 120 mothers of neonates in which n=60 cases were Mothers of the neonates with congenital hypothyroidism (TSH > 15.2 µIU/mL) and n=60 controls mothers of euthyroid healthy neonates (TSH ≤ 15.2 µIU/mL). Data collected regarding the maternal thyroid status was evaluated in the antenatal period during first trimester and neonatal thyroid status was evaluated at birth from cord blood. All the mothers included in the study with hypothyroidism (both cases and controls) were either already on treatment or were treated appropriately during pregnancy**.** The mean maternal age in cases (n=60) was 34.8± 5.7 years while that in control (n=60) was 25.43± 4.3 years. There is a high statistically significant (p<0.0001) increase in maternal age in cases compared to controls. The odds of being ≥35 years were higher in mothers of neonates with congenital hypothyroidism as compared to mothers of normal children with Odds ratio of 5.06; and highly significant P value 0.0001. The odds of mothers of neonates with congenital hypothyroidism having hypothyroidism, compared mothers of euthyroid neonates having hypothyroidism is not statistically significant with Odds ratio of 3.14; with P value 0.06. The risks of acquiring congenital hypothyroidism in neonates increase with advanced maternal age. Neonatal TSH levels are dynamic and are affected by several factors including maternal hypothyroidism. Pre-conceptional consultation and evaluation of thyroid status as well as first trimester universal screening and adequate treatment of maternal hypothyroidism may play an effective role in decreasing the incidence of neonatal congenital hypothyroidism, especially in high risk pregnancies due to advanced maternal age.

Keywords: Kerala neonates, advanced maternal age, hypothyroidism in neonates, universal neonatal screening, parental screening, Dyshormonogenesis

Introduction:

Congenital hypothyroidism(CH) is the most common neonatal endocrine disorder. Studies have reported a incidence of around 1:3000 to 1:4000 live new-born's globally[(1)], the prevalence of congenital hypothyroidism varies across countries and different geographic regions. It is higher in Hispanic and East Asia than in Western countries and lower in blacks. There is a 2:1 greater incidence in females compared with males and there is an increased risk in infants with Down's syndrome [(2)]. The congenital hypothyroidism prevalence in India was estimated at 5.7 per 10,000 infants [(3)] with an incidence rate of 1 in 244 in Kerala state [(4)].

Neonatal mass screening programs provide the best tool for early diagnosis. Since the establishment of the congenital hypothyroidism screening program in Quebec and Pittsburgh in 1974, neonatal screening has been routinely implemented in developed as well as some developing countries by measuring Thyroid-Stimulating Hormone (TSH) and thyroxine (T4) through cord blood and heel blood samples and have been largely successful in diagnosis and prevention of intellectual disability in these infants[(5)].

Up to 2% of thyroid dysgenesis is familial. Congenital hypothyroidism caused by organification defects is often recessively inherited[(6)]. Thyroid dysgenesis accounts for approximately 80% to 85% of cases and dyshormonogenesis account for 10-15% of cases[(7)]. Congenital hypopituitarism and isolated

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

deficiency of TSH are possible causes of secondary congenital hypothyroidism. Transient CH most commonly occurs in preterm infants born in areas of endemic iodine deficiency. Teenage mothers have a higher risk of preterm birth along with other issues such as low birth weight, low Apgar score and postnatal mortality[8].

Both extremes of the reproductive age are considered at risk for adverse pregnancy outcomes[9]. Delayed childbearing carries a higher risk of maternal and obstetric complications, such as the development of pathologies during pregnancy, the type of birth, as well as other parameters related to the pregnancy, labour, and delivery [9]. Advanced maternal age is defined as childbearing in a woman over 35 years of age[10]. The studies related to the role of maternal age as a risk factor for development of congenital hypothyroidism are very minimal. Various effects of maternal subclinical gestational hypothyroidism on fetal development have been studied widely, whereas, not much studies are available which analyse the association of adequately treated maternal hypothyroidism on the neonatal thyroid dysgenesis and other causes of congenital hypothyroidism on infants.

With this background this current study intends to observe the maternal age and thyroid status and its association with neonatal congenital hypothyroidism.

Methodology:

This study collected data about the age and thyroid status of 120 mothers of neonates from the period of July 2019 till February 2020 from the neonatal screening program for thyroid disorders at DM Wayanad institute of medical sciences, Wayanad, Kerala.

60 Mothers of the neonates with TSH > 15.2 µIU/mL were included in the study as cases. 60 mothers of euthyroid healthy neonates were included as control group with TSH ≤ 15.2 µIU/mL.

Mothers of neonates with Cardiac dysfunction, Blood cell disorders (anaemia, Rh disease, thalassemia), GI disorders, Respiratory distress, Pneumonia, Chronic lung disease, Neural tube defects, Congenital infections (HIV, rubella, chickenpox, syphilis, herpes) and Lactose intolerance were excluded from the study.

Data collected regarding the maternal thyroid status was evaluated in the antenatal period during first trimester and neonatal thyroid status was evaluated at birth from cord blood. TFT, FT4 and FT3 were estimated by Electro Chemi Luminescence Immuno Assay (ECLIA) on the Roche cobas e 411 analyzer. GraphPad Prism 9 software was used for statistical analysis. **Results:**

A total of 120 subjects were included in the present study, out of which 60 were mothers with congenital hypothyroid neonates (case) and 60 were mothers with healthy neonates (control).

Table 1: Comparison of neonatal TSH between case and controls

	Cases (n=60)		Control (n=60)	
TSH (µIU/mL)	Mean	SD	Mean	SD
	19.39	3.21	6.53	3.07

Table 1 shows the difference in mean TSH levels (µIU/mL) between cases (19.39 ± 3.21) and control (6.53± 3.07)

Table 2: Maternal age in case and control

GROUPS		MATERNAL AGE (Year)		
	N	MEAN	SD	p value
CASE	60	34.8	5.7	< 0.0001
CONTROL	60	25.43	4.3	

Table 2 shows that maternal age in case (n=60) with mean ± SD is 34.8± 5.7 years while that in control (n=60) with mean ±SD is 25.43± 4.3 years.

There is a high statistically significant ($p<0.0001$) increase in advanced maternal age in case compared to controls.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Figure1: Maternal age in cases

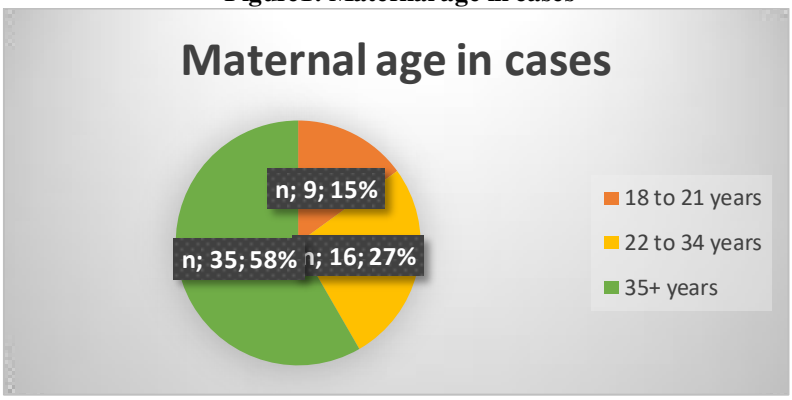

Figure 2: Maternal age in controls

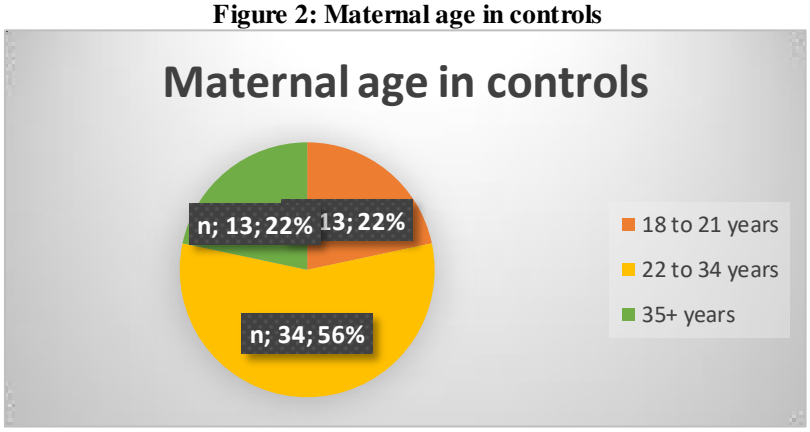

Figure 1& 2 shows maternal age distribution in case and control. The mean maternal age in cases (n=60) was 34.8± 5.7 years while that in control (n=60) was 25.43± 4.3 years. There is a high statistically significant (p<0.0001) increase in maternal age in cases compared to controls.

Table 3: Comparison of maternal age and neonatal TSH between cases and controls

GROUPS	AGE(YEAR)	n	MATERNAL AGE (YEAR)		Neonatal TSH (µIU/mL)	
			MEAN	SD	MEAN	SD
CASE	≥35	35	33.89	2.26	19.47	3.15
	22-34	17	24.06	3.9	19.23	3.24
	18-21	8	24.13	3.72	19.32	3.84
CONTROL	≥35	13	31.77	1.09	8.1	1.36
	22-34	31	24.52	2.42	6.31	3.36
	18-21	16	20.44	3.29	5.69	3.16

Table 3 shows the comparison of maternal age and TSH in both cases and controls.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Table 4: Odds ratio of mothers of neonates with CHT aged above 30

GROUPS	AGE (years)	N	ODDS RATIO
CASE (n=60)	≥35	35	5.06
	<34	25	
CONTROL (n=60)	≥35	13	
	<34	47	

Table 4 indicates that the odds of being ≥35 years were higher in mothers of neonates with congenital hypothyroidism as compared to mothers of normal children with Odds ratio of 5.06; 95% CI: 2.27–11.27, z statistic 3.971, Significance level P = 0.0001

Figure 3: Thyroid status of mothers in case and controls

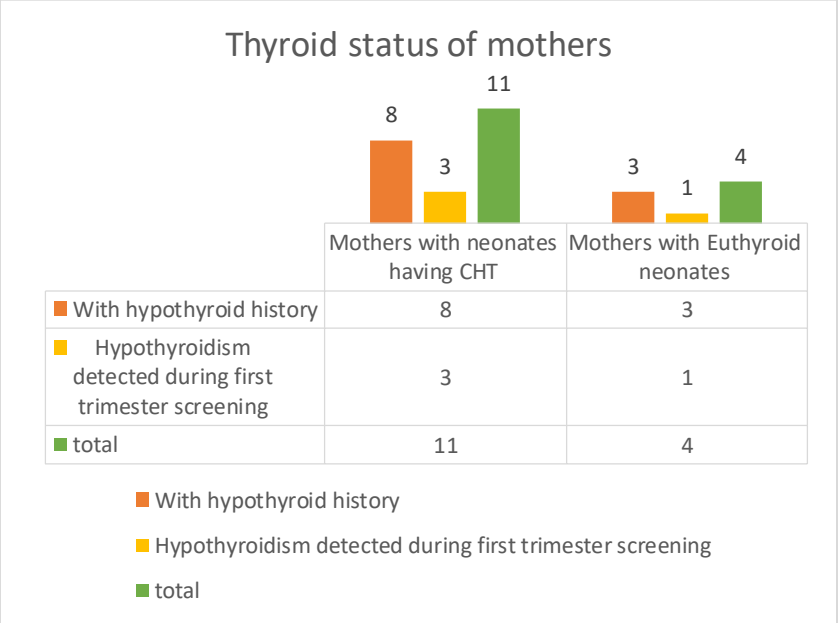

Figure 3 shows the thyroid status of mothers of neonates with congenital hypothyroidism (cases) and mothers of euthyroid neonates. The maternal thyroid status was evaluated in the antenatal period during the first trimester. Out of 60 cases, a total 11 mothers either had the history of hypothyroidism or were diagnosed during the first trimester tests compared to 4 mothers with similar Thyroid status out of the 60 controls.

Table 5: Odds ratio of hypothyroid mothers and euthyroid mothers between cases and controls

Groups	Mothers with hypothyroidism	Euthyroid mothers	Odds ratio
Mothers of neonates with congenital hypothyroidism (n = 60)	11	49	3.14
Mothers of euthyroid neonates (n = 60)	4	56	

Table 5, shows that the odds of mothers of neonates with congenital hypothyroidism having hypothyroidism, compared mothers of euthyroid neonates having hypothyroidism is not statistically significant with Odds ratio of 3.14; 95 % CI: 0.9401 to 10.5070 , z statistic 1.860, Significance level P = 0.06

All the mothers included in the study with hypothyroidism (both cases and controls) were either already on treatment or were treated appropriately during pregnancy.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Discussion:

In the current study, we observed that the mean age of the mothers of neonates with congenital hypothyroidism (34.8±5.7) was higher when compared to the mothers of neonates who were euthyroid (25.43 ± 4.3) with a highly significant p value of < 0.0001. In the current study, cord blood was analysed to detect the TSH values at birth as a screening tool for congenital hypothyroidism in neonates. In a similar study conducted in Chinese neonates, by Pianpian fan et al, observed the association of advanced maternal age with lower fetal FT3 in the cord blood of neonates born by C-section deliveries [11]. Many studies [12,13,14, 15, 16, 17] have approved the use of cord blood TSH as a screening tool. While heel prick sample is generally considered ideal, there are many variable factors affecting the consistency of such sample such as the blood collection timing, differences in sample collection procedures and temperature factor [18,19]. Ideally an universal screening at 3 to 4 days should be done for detecting congenital hypothyroidism[20]. Cord blood TSH has shown consistent results compared to heel prick TSH[21]. However, since, we have not done any follow up study, we may not be able to determine if the CHT detected in such neonates is of transient or permanent nature[7].

Furthermore, in the current study, 58% of mothers of neonates with congenital hypothyroidism were ≥35years old compared to 22% in the control group. Even though the sample size is small, the study observes that the odds of being ≥35 years were significantly higher in mothers of children with congenital hypothyroidism as compared to mothers of euthyroid neonates. It has been found that oocyte aneuploidy occurs more due to meiotic cohesions that are found to be associated more with advanced maternal age[22]. Devi Dayal et al, observed association of advanced maternal age with gene encoding mutations that are related to thyroid gland development [23]. Incidence of increased operative deliveries in the form of caesarean sections, as well as operative vaginal births (due to prolonged second stage of labor) occur more in mothers with advanced maternal age[24]. The various medical as well as obstetric high risk factors which are common in increased maternal age- such as , gestational diabetes mellitus , hypertension in pregnancy ,high maternal BMI, multiple gestation, IUGR , and non-reassuring fetal heart rate in second stage of labor , can contribute to the intrapartum stress[25, 26, 27, 28,29,30] which is frequently associated with decreased levels of thyroid hormone distributor proteins such as albumin, transthyretin, thyroxine binding globulin [31].

Maternal hypothyroidism has great potential to jeopardize the maternal and fetal health. Of the 120 mothers included in the study as case and control, 11 had history of hypothyroidism prior to conception and 4 were diagnosed with hypothyroidism during the first trimester screening. All these mothers were treated adequately and were maintained as euthyroid throughout the course of antenatal period. In the current study, when we analysed the association of maternal hypothyroidism and neonatal CHT we observed p value of 0.06 , that implies no statistical significance, which may be due to the fact that all mothers were adequately treated in the antenatal period. Furthermore the lack of statistical significance could be contributed due to the comparatively small sample size. Untreated maternal hypothyroidism has varied effects on the fetal growth and the neonatal outcomes such as early abortions, still birth, preterm birth, low birth weight, respiratory distress syndrome and lower mean intelligence & learning abilities in children of such mothers.

Conclusion:

The risks of acquiring congenital hypothyroidism in neonates increase with advanced maternal age. Neonatal TSH levels are dynamic and are affected by several factors including maternal hypothyroidism. Pre-conceptional consultation and evaluation of thyroid status as well as first trimester universal screening and adequate treatment of maternal hypothyroidism may play an effective role in decreasing the incidence of neonatal congenital hypothyroidism, especially in high risk pregnancies due to advanced maternal age.

Further research with a bigger sample size on the identification of the cofounders, such as, increase in new mutations in gene encoding transcription factors associated with thyroid gland development, may prove to be helpful for assessing the status of neonatal thyroid development.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

References:

1. Unnikrishnan AG, Vyas U. Congenital hypothyroidism - An Indian perspective. Thyroid Res Pract 2017;14:99-105.
2. Agrawal P, Philip R, Saran S, Gutch M, Razi MS, Agroiya P, Gupta K. Congenital hypothyroidism. Indian J Endocr Metab 2015;19:221-7.
3. Deng K, He C, Zhu J, Liang J, Li X, Xie X, Yu P, Li N, Li Q, Wang Y. Incidence of congenital hypothyroidism in China: data from the national newborn screening program, 2013-2015. J Pediatr Endocrinol Metab. 2018 Jun 27;31(6):601-608. doi: 10.1515/jpem-2017-0361. PMID: 29715190.
4. Anand MR, Ramesh P, Nath D. Congenital Hypothyroidism Screening with Umbilical Cord Blood: Retrospective Analysis. Indian Pediatr. 2015 May;52(5):435-6. doi: 10.1007/s13312-015-0652-8. PMID: 26061935.
5. Khammarnia M, Siakhulak FR, Ansari H, Peyvand M. Risk factors associated with congenital hypothyroidism: a case-control study in southeast Iran. Electron Physician. 2018 Feb 25;10(2):6286-6291. doi: 10.19082/6286. PMID: 29629049; PMCID: PMC5878020.
6. Roberts HE, Moore CA, Fernhoff PM, Brown AL, Khoury MJ. Population study of congenital hypothyroidism and associated birth defects, Atlanta, 1979-1992. Am J Med Genet 1997;71:29-32.
7. Rastogi, M.V., LaFranchi, S.H. Congenital hypothyroidism. Orphanet J Rare Dis **5,** 17 (2010). https://doi.org/10.1186/1750-1172-5-17.
8. Londero AP, Rossetti E, Pittini C, Cagnacci A, Driul L. Maternal age and the risk of adverse pregnancy outcomes: a retrospective cohort study. BMC pregnancy and childbirth. 2019 Dec 1;19(1):261.
9. Molina-García L, Hidalgo-Ruiz M, Cámara-Jurado AM, Fernández-Valero MJ, Delgado-Rodríguez M, Martínez-Galiano JM. Newborn Health Indicators Associated with Maternal Age during First Pregnancy. International journal of environmental research and public health. 2019 Jan;16(18):3448.
10. Casteleiro A, Paz-Zulueta M, Parás-Bravo P, Ruiz-Azcona L, Santibañez M. Association between advanced maternal age and maternal and neonatal morbidity: A cross-sectional study on a Spanish population. PloS one. 2019;14(11).
11. Fan P, Luo ZC, Tang N, Wang W, Liu Z, Zhang J, Ouyang F. Advanced Maternal Age, Mode of Delivery, and Thyroid Hormone Levels in Chinese Newborns. Front Endocrinol (Lausanne). 2020 Jan 10;10:913. doi: 10.3389/fendo.2019.00913. PMID: 31998241; PMCID: PMC6966407.
12. Bhatia R, Rajwaniya D. Congenital Hypothyroidism Screening in Term Neonates using Umbilical Cord Blood TSH Values. Indian J Endocrinol Metab. 2018 Mar-Apr;22(2):277-279. doi: 10.4103/ijem.IJEM_640_17. PMID: 29911045; PMCID: PMC5972488.
13. Fagela-Domingo C, Padilla CD, Cutiongco EM. Screening for congenital hypothyroidism (CH) among Filipino newborn infants. Philippine Newborn Screening Study Group. Southeast Asian J Trop Med Public Health. 1999;30 Suppl 2:20-2. PMID: 11405206.
14. Azizi F, Oladi B, Nafar Abadi M T, Haji Pour R. Screening for detection of Congenital Hypothyroidism in Tehran: Effect of Iodine Deficiency on Transient Elevation of TSH in Children. Research in Medicine. 1994; 18 (1) :34-38.
15. Ordookhani A, Mirmiran P, Najafi R, Hedayati M, Azizi F. Congenital hypothyroidism in Iran. Indian J Pediatr. 2003 Aug;70(8):625-8. doi: 10.1007/BF02724251. PMID: 14510082.
16. Wu LL, Sazali BS, Adeeb N, Khalid BA. Congenital hypothyroid screening using cord blood TSH. Singapore Med J. 1999 Jan;40(1):23-6. PMID: 10361481.
17. Ford G, LaFranchi SH. Screening for congenital hypothyroidism: a worldwide view of strategies. Best Pract Res Clin Endocrinol Metab. 2014 Mar;28(2):175-87. doi: 10.1016/j.beem.2013.05.008. Epub 2013 Jun 18. PMID: 24629860.
18. Clapin H, Lewis BD, Greed L, Dawkins H, O'Leary P. Factors influencing neonatal thyroid-stimulating hormone concentrations as a measure of population iodine status. J Pediatr Endocrinol Metab. 2014 Jan;27(1-2):101-6. doi: 10.1515/jpem-2013-0189. PMID: 24057593.
19. Ryckman KK, Berberich SL, Shchelochkov OA, Cook DE, Murray JC. Clinical and environmental influences on metabolic biomarkers collected for newborn screening. Clinical Biochemistry. 2013 Jan;46(1-2):133-138. DOI: 10.1016/j.clinbiochem.2012.09.013.
20. Manglik AK, Chatterjee N, Ghosh G. Umbilical cord blood TSH levels in term neonates: a screening tool for congenital hypothyroidism. Indian Pediatr. 2005 Oct;42(10):1029-32. PMID: 16269841.
21. Guoqing W, Yada M, Xiaozhong L, Derong Q. Association between cord blood and heel blood TSH levels. Modern Prevent Med. (2004) 31:64 10.3969/j.issn.1003-8507.2004.01.027.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

22. Chiang T, Schultz RM, Lampson MA. Meiotic origins of maternal age-related aneuploidy. Biol Reprod. 2012 Jan 10;86(1):1-7. doi: 10.1095/biolreprod.111.094367. PMID: 21957193; PMCID: PMC3313661.
23. Dayal D, Sindhuja L, Bhattacharya A, Bharti B. Advanced maternal age in Indian children with thyroid dysgenesis. Clin Pediatr Endocrinol. 2015 Apr;24(2):59-62. doi: 10.1297/cpe.24.59. Epub 2015 May 15. PMID: 26019402; PMCID: PMC4436557.
24. Rydahl E, Declercq E, Juhl M, Maimburg RD. Cesarean section on a rise-Does advanced maternal age explain the increase? A population register-based study. PLoS One. 2019 Jan 24;14(1):e0210655. doi: 10.1371/journal.pone.0210655. PMID: 30677047; PMCID: PMC6345458.
25. Cohen W. Does maternal age affect pregnancy outcome? BJOG. 2014 Feb;121(3):252-4. doi: 10.1111/1471-0528.12563. PMID: 24428449.
26. Richards MK, Flanagan MR, Littman AJ, Burke AK, Callegari LS. Primary cesarean section and adverse delivery outcomes among women of very advanced maternal age. J Perinatol 2016;36:272–7. 10.1038/jp.2015.204.
27. Oakley L, Penn N, Pipi M, Oteng-Ntim E, Doyle P. Risk of Adverse Obstetric and Neonatal Outcomes by Maternal Age: Quantifying Individual and Population Level Risk Using Routine UK Maternity Data. PLoS One 2016;11:e0164462 10.1371/journal.pone.0164462.
28. Timofeev J, Reddy UM, Huang CC, Driggers RW, Landy HJ, Laughon SK. Obstetric complications, neonatal morbidity, and indications for cesarean delivery by maternal age. Obstet Gynecol 2013;122:1184–95. 10.1097/AOG.0000000000000017.
29. Herstad L, Klungsoyr K, Skjaerven R, Tanbo T, Forsen L, Abyholm T, et al. Maternal age and emergency operative deliveries at term: a population-based registry study among low-risk primiparous women. BJOG 2015;122:1642–51. 10.1111/1471-0528.12962.
30. Omih EE, Lindow S. Impact of maternal age on delivery outcomes following spontaneous labour at term. J Perinat Med 2016;44:773–7. 10.1515/jpm-2015-0128
31. Rabah SA, Gowan IL, Pagnin M, Osman N, Richardson SJ. Thyroid hormone distributor proteins during development in vertebrates. Front Endocrinol. (2019) 10:506. 10.3389/fendo.2019.00506.