

·临床研究·

28~36周早产儿出生后3~21天血FT3、FT4、TSH变化分析

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摘要:【目的】分析28~36周早产儿出生后3~21 d FT3、FT4、TSH变化的特征。【方法】回顾性分析2018年7月至2019年6月中山大学附属第三医院新生儿科住院的236例28~36周早产儿的临床资料,包括甲状腺功能检查(FT3、FT4和TSH)、胎龄、性别、出生体质量、出生身长、检查日龄、辅助生殖方式、单胎或多胎、母亲甲状腺疾病和母亲妊娠期糖尿病,比较早产儿3~7 d与8~21 d FT3、FT4和TSH水平的差异;分析影响早产儿FT3、FT4和TSH水平的独立因素;比较不同胎龄早产儿FT3、FT4和TSH水平差异。【结果】早产儿3~7 d FT3水平(3.23±0.54) pmol/L,低于8~21 d的(3.41±0.76) pmol/L,差异有统计学意义($P=0.040$);早产儿3~7 d的FT4水平(15.36±3.40) pmol/L,高于8~21 d的(13.20±2.63) pmol/L,差异有统计学意义($P<0.001$);3~7 d与8~21 d的TSH分布的差异没有统计学意义($P=0.846$);早产儿3~7 d FT3水平受到胎龄的影响($P<0.001$),3~7天FT4水平受到胎龄和检查日龄的影响($P<0.001$),8~21 d的FT3、FT4水平均受到胎龄和性别的影响($P<0.001$, $P<0.001$);3~7 d、8~21 d的FT3、FT4水平与胎龄为正相关($P<0.001$, $P<0.001$; $P<0.001$, $P=0.001$)。【结论】胎龄影响出生后3~21 d早产儿的甲状腺功能,胎龄越小,FT3、FT4越低,需要建立一个胎龄相关的FT4或T4参考范围,结合TSH联合评估甲状腺功能。

关键词:早产儿;三碘甲状腺原氨酸;四碘甲状腺原氨酸;促甲状腺素

中图分类号:R72

文献标志码:A

文章编号:1672-3554(2021)04-0581-08

DOI: 10.13471/j.cnki.j.sun.yat-sen.univ(med.sci).2021.0414

Changes in FT3, FT4 and TSH Levels in 3~21-day-old Preterm Infants Born at 28~36 Weeks of Gestation

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Abstract: 【Objective】 To analyze the changes of serum levels of free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) in 3~21-day-old preterm infants born between 28 and 36 weeks of gestation. 【Methods】 We retrospectively reviewed the clinical data of 236 preterm infants born at 28~36 weeks of gestation in the third affiliated hospital of Sun Yat-sen university between July 2018 and June 2019. The clinical data included thyroid function parameters (FT3, FT4, TSH), gestational age, gender, birth weight, birth length, time of examination, mode of conception, singleton or multiple birth, maternal thyroid disease and maternal gestational diabetes mellitus (GDM). FT3, FT4 and TSH levels between 3~7-day-old and 8~21-day-old preterm infants were compared. Multiple linear regression models were used to identify the independent factors affecting FT3, FT4 and TSH levels. FT3 and FT4 levels in different gestational age groups were compared. 【Results】 Compared with those in 8~21-day-old preterm infants, in 3~7-day-old preterm infants, FT3 levels were significantly lower [(3.23±0.54) pmol/L vs. (3.41±0.76) pmol/L, $P=0.040$] and FT4 levels were significantly higher [(15.36±3.40) pmol/L vs. (13.20±2.63) pmol/L, $P<0.001$]. No statistical difference was

收稿日期:2021-01-11

基金项目:广东省科技计划项目(2014A020212392)

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found in TSH levels. ($P=0.846$). In 3~7-day-old preterm infants, FT3 levels were associated with gestational age ($P < 0.001$); FT4 levels were associated with gestational age and time of examination ($P < 0.001$). In 8~21-day-old preterm infants, both FT3 and FT4 levels were associated with gestational age and gender ($P < 0.001$, $P < 0.001$). FT3 and FT4 were positively correlated with gestational age in both groups ($P < 0.001$, $P < 0.001$; $P < 0.001$, $P = 0.001$).【Conclusion】 Gestational age affects the thyroid function of the preterm infants of 3~21 days. The younger the gestational age, the lower FT3 and FT4 levels. A reference range of FT4 or T4 related to gestational age should be established, combined with TSH, to evaluate the thyroid function in preterm infants.

Key words: preterm infants; free triiodothyronine (FT3); free thyroxine (FT4); thyroid-stimulating hormone (TSH)

[J SUN Yat-sen Univ (Med Sci), 2021, 42(4): 581-588]

先天性甲状腺功能减退(congenital hypothyroidism, CH)是导致儿童智力发育迟缓的最常见病因之一。CH的发病率为1/3 000~1/4 000^[1],早期诊断是预防该症致智力障碍最重要的举措。2017年我国新生儿CH筛查覆盖率已经超过97%,发病率约为1/2 050^[2]。早产儿甲状腺功能障碍的发生率高于足月儿,并随着早产儿存活率的提高而增加。体质量<1 500 g的早产儿CH发病率报道从1/7到1/324不等^[3]。目前临床上缺乏不同胎龄早产儿甲状腺激素水平的参考范围,对于早产儿甲状腺功能的特征掌握不足,对甲状腺功能评估有较多争议。现就2018至2019年中山大学附属第三医院收治的早产儿甲状腺检查资料进行分析,旨在了解早产儿不同胎龄的甲状腺功能差异、影响因素和出生后随时间变化的特征。

1 材料与方法

1.1 研究对象

回顾性收集2018年7月1日至2019年6月30日在中山大学附属第三医院新生儿科住院,且行甲状腺功能检查的28~36周早产儿的临床资料。纳入标准:胎龄28~36周;出生后3~21 d在本院行甲状腺功能检查。剔除标准:外观上的明显缺陷如特殊面容、唇裂、性发育障碍等,住院期间已明确的染色体疾病或基因异常;检查前发生过呼吸窘迫综合征、心功能不全、其他各种病因需要有创呼吸支持者;两次及以上静脉血糖<2.2 mmol/L;检查前使用过多巴胺、糖皮质激素;检查前使用过左旋甲状腺素片。本研究取得本院伦理委员会审核豁免知情同意。

1.2 方法

通过医院电子病例系统,收集胎龄、性别、出生体质量、出生身长、检查日龄、是否多胎妊娠、是否采用辅助生殖方式所生、母亲甲状腺疾病、母亲妊娠期糖尿病(gestational diabetes mellitus, GDM)、游离三碘甲状腺原氨酸(free triiodothyronine, FT3)、游离甲状腺素(free tetraiodothyronine, FT4)和促甲状腺素(thyroid stimulating hormone, TSH)。

受试者的FT3、FT4和TSH血样采用股静脉血1.5 mL进行化学发光微粒子免疫检测法测定。该项检查为患者诊疗所需,结果已在电子病例系统中可查询。

指南推荐足月新生儿筛查的最佳时间是48~72 h,早产儿可以延长至生后7 d内。我科大部分的早产儿在生后≥48 h~7 d完成了第1次甲状腺功能检查,其中部分病例在生后2~3周完成了第2次甲状腺检查。有小部分早产儿因为体质量轻导致的采血限制,在生后2~3周之间才进行第1次甲状腺检查。据报道早产儿在生后第1周甲状腺激素水平有别于生后2~4周,在生后2~4周,FT4、TSH值变化较为平缓^[4-5]。故本研究中按检查日龄分为3~7 d(≥48 h~7 d)和8~21 d(2~3周)组。

1.3 统计学分析

采用SPSS 22.0软件进行统计分析。采用独立样本 t 检验3~7 d组和8~21 d组FT3、FT4差异;箱线图判断异常值,Shapiro-Wilk检验数据正态性,Levene's检验方差齐性。不符合正态分布的两组间比较用Mann-Whitney U 检验。采用多重线性回归,基于胎龄、性别、检查日龄、小于胎龄儿、人工辅助生殖技术、多胎、母亲甲状腺疾病和母亲GDM,以上8个因子,预测影响早产儿甲状腺功能的独立因素;Dubin-Watson值检测观测值独立性;部分回

归散点图、学生化残差与预测值散点图判断自变量和因变量的线性关系;学生化残差与未标化的预测值的散点图判断数据等方差性;回归容忍度和膨胀因子判断多重共线性;标准化残差直方图和P-P图验证残差正态分布;残差不满足方差齐性时采取加权最小二乘法拟合进行回归分析。采用Pearson相关分析FT3、FT4水平与胎龄的相关关系。采用单因素方差分析不同胎龄早产儿FT3、FT4的差异。

2 结果

2.1 基本资料

共收集到236例早产儿资料,209例在3~7 d内第1次行甲状腺功能检查,排除出院、严重疾病、有创呼吸支持、应用多巴胺、糖皮质激素和左旋甲状腺素片因素后,当中32例在8~21 d期间的第2次甲状腺功能检查结果纳入统计,在8~21 d间还有27例早产儿第1次甲状腺功能检查结果纳入分析。基本资料详见表1。

2.2 28~36周早产儿3~7 d和8~21 d甲状腺功能检查的差异

用Mann-Whitney *U*检验两组胎龄,两组胎龄分布近似(图1)。3~7 d组中位数为34周,8~21 d组中位数为33周,差异有统计学意义, $Z=-2.502, P=0.010$ 。

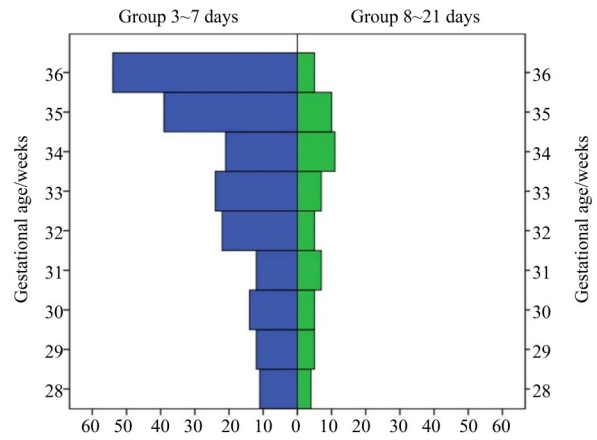


图1 早产儿3~7天组和8~21天组胎龄分布

Fig. 1 Distribution of gestational age of preterm infants in two groups

用独立样本 *t* 检验,3~7 d组FT3水平(3.23±0.54) pmol/L 低于8~21 d组(3.41±0.76) pmol/L,差值为-0.18 [95%CI为(-0.36, -0.08)], $t=-2.062, P=0.040$ 。

用独立样本 *t* 检验,3~7 d组FT4水平(15.36±3.40) pmol/L 高于8~21 d组(13.20±2.63) pmol/L,差值为2.16 [95%CI为(1.22, 3.10)], $t=4.512, P<0.001$ 。

用Mann-Whitney *U*检验,3~7 d组TSH中位数2.19 U/mL,8~21 d组TSH中位数2.42 U/mL,2组TSH的差异没有统计学意义, $Z=-0.194, P=0.846$ 。

表1 236例早产儿基本资料

Table1 Basic data of 236 preterm infants

$[(\bar{x}\pm s), n, N(n)]$

Items	3~7 days(n=209)	8~21 days(n=59)
Time of examination /d	4.31±1.19	11.75 ±3.74
Gender /n		
Female	115	31
Male	94	28
SGA /n	16	9
Conceived by assisted reproductive technique/n	16	6
Singleton births/n	155	44
Multiple births/n	54	15
Maternal thyroid disease/n		
Hypothyroidism(Euthyrox treatment)	9(5)	1(0)
Hyperthyroidism(ATD treatment)	4(0)	0
Maternal GDM/n	32	10

SGA: small for gestational age infant; ATD: antithyroid drugs; GDM: gestational diabetes mellitus.

2.3 影响28~36周早产儿出生后3~7 d FT3、FT4水平的独立因素

采用逐步回归,分析胎龄、性别、检查日龄、小于胎龄儿、多胎妊娠、采用辅助生殖方式所生、母亲甲状腺疾病和母亲GDM对早产儿3~7 d FT3水平的影响,最终模型仅纳入胎龄1个变量,具有统计学意义($F=74.846, P<0.001$),模型参数估计结果见表2,胎龄可以解释FT3水平变异的26.7%。

采用逐步回归,分析胎龄、性别、检查日龄、小于胎龄儿、多胎妊娠、采用辅助生殖方式所生、母亲甲状腺疾病和母亲GDM对早产儿3~7 d FT4水平的影响,最终模型纳入胎龄和检查日龄2个变量($F=64.555, P<0.001$),模型参数估计结果见表3,早产儿3~7 d FT4水平受到胎龄和检查日龄的影响,胎龄对FT4影响最大。

2.4 影响28~36周早产儿出生后8~21 d FT3、FT4水平的独立因素

采用逐步回归,分析胎龄、性别、检查日龄、小于胎龄儿、多胎妊娠、采用辅助生殖方式所生、母亲甲状腺疾病和母亲GDM对早产儿8~21 d FT3水平的影响,最终模型纳入胎龄和性别2个变量($F=17.481, P<0.001$),模型参数估计结果见表4,早产儿8~21 d FT3水平受到胎龄和性别的影响,胎龄对FT3影响最大。

采用逐步回归,分析胎龄、性别、检查日龄、小于胎龄儿、多胎妊娠、采用辅助生殖方式所生、母亲甲状腺疾病和母亲GDM对早产儿8~21 d FT4水平的影响,最终模型纳入胎龄和性别2个变量($F=9.676, P<0.001$),模型参数估计结果见表5,早产儿8~21 d FT4水平受到胎龄和性别的影响,胎龄对FT4影响最大。

表2 早产儿出生后3~7 d FT3水平回归模型的参数估计结果

Table 2 Parameter estimation results of FT3 regression model in 3~7 days

Variables	Degree of freedom	Unstandardized Coefficients	Standard Error	<i>t</i>	<i>P</i>	Standardized Coefficients
Constant	1	-0.824	0.473	-1.742	0.083	
Gestational age	1	0.122	0.014	8.651	<0.001	0.516

$R^2=0.267, F_{(1,206)}=74.846, P<0.001, \text{Adjusted } R^2=0.263.$

表3 早产儿出生后3~7 d FT4水平回归模型的参数估计结果

Table 3 Parameter estimation results of FT4 regression model in 3~7 days

Variables	Degree of freedom	Unstandardized Coefficients	Standard Error	<i>t</i>	<i>P</i>	Standardized Coefficients
Constant	1	-6.850	2.703	-2.534	0.012	
Gestational age	1	0.749	0.078	9.655	<0.001	0.531
Time of examination	1	-0.620	0.124	-4.995	<0.001	-0.275

$R^2=0.386, F_{(2,205)}=64.555, P<0.001, \text{Adjusted } R^2=0.380.$

表4 早产儿出生后8~21 d FT3水平回归模型的参数估计结果

Table 4 Parameter estimation results of FT3 levels regression model in 8~21 days

Variables	Degree of freedom	Unstandardized Coefficients	Standard Error	<i>t</i>	<i>P</i>	Standardized Coefficients
Constant	1	-1.556	1.110	-1.402	0.166	
Gestational age	1	0.159	0.033	4.761	<0.001	0.508
Gender	1	-0.411	0.161	-2.551	0.014	-0.272

$R^2=0.384, F_{(2,56)}=17.481, P<0.001, \text{Adjusted } R^2=0.362.$

表5 早产儿出生后8~21 d FT4水平回归模型的参数估计结果
Table 5 Parameter estimation results of FT4 levels regression model in 8~21 days

Variables	Degree of freedom	Unstandardized Coefficients	Standard Error	<i>t</i>	<i>P</i>	Standardized Coefficients
Constant	1	1.236	4.217	0.293	0.770	
Gestational age	1	0.392	0.127	3.087	0.003	0.362
Gender	1	-1.528	0.612	-2.499	0.015	-0.293

$R^2=0.257, F_{(2,56)}=9.676, P<0.001, \text{Adjusted } R^2=0.230.$

2.5 影响28~36周早产儿出生后3~7 d TSH水平的独立因素

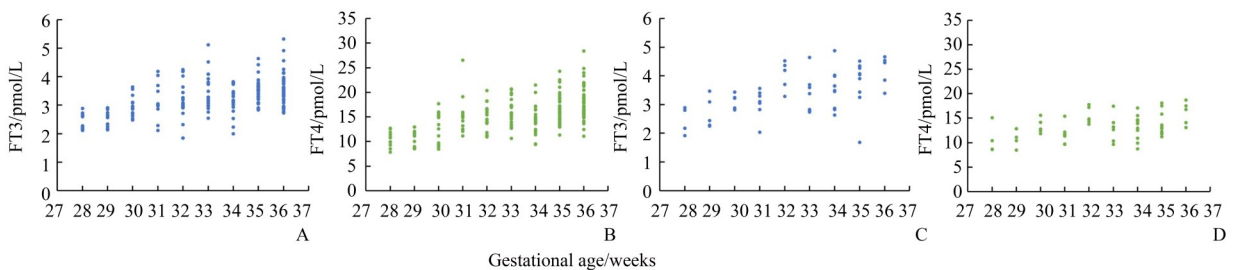
用多重线性回归,分析胎龄、性别、检查日龄、小于胎龄儿、多胎妊娠、采用辅助生殖方式所生、母亲甲状腺疾病和母亲GDM对早产儿3~7 d TSH水平的影响,模型 $F_{(8,199)}=0.228, P=0.985$,不具有统计意义,以上因素均不是影响因素。

用多重线性回归,分析胎龄、性别、检查日龄、小于胎龄儿、多胎妊娠、采用辅助生殖方式所生、母亲甲状腺疾病和母亲GDM对早产儿8~21 d TSH水平的影响,因残差不满足方差齐性,对胎龄加权后采用加权最小二乘法拟合的线性回归模型, $F_{(8,50)}=$

1.433, $P=0.206$,不具有统计意义,以上因素均不是独立影响因素。

2.6 28~36周早产儿FT3、FT4水平与胎龄的相关性

如图2所示,早产儿胎龄与FT3、FT4存在线性关系。3~7 d、8~21 d FT3与胎龄、FT4与胎龄均存在正相关关系。生后3~7 d,不同胎龄的FT3差异有统计学意义, $P<0.001$,不同胎龄的FT4差异具有统计学意义, $P<0.001$ 。生后8~21 d,不同胎龄的FT3水平差异具有统计学意义, $P<0.001$,不同胎龄的FT4水平差异有统计学意义, $P=0.001$ (表6)。各组间两两比较见表7。



A and B present FT3 and FT4 in 3~7 d; C and D present FT3 and FT4 in 8~21 d.

图2 早产儿FT3、FT4与胎龄的线性关系

Fig. 2 Linear relationships between FT3、FT4 and gestational age in preterm infants

表6 早产儿FT3、FT4与胎龄的简单线性相关分析结果
Table 6 Analysis of correlation between FT3、FT4 and gestational age (pmol/L)

Age of examination	3~7 d (n=207)		8~21 d (n=59)	
	FT3	FT4	FT3	FT4
<i>r</i>	0.532	0.592	0.559	0.417
<i>t</i>	9.000	10.530	5.094	3.465
<i>P</i>	<0.001	<0.001	<0.001	0.001

Two outliers were not included in the statistics.

表7 早产儿不同胎龄间FT3、FT4的差异
Table 7 Comparison of FT3, FT4 between different gestational ages (pmol/L)

Gestational age	3~7 d (n=207)		8~21 d (n=59)	
	FT3	FT4	FT3	FT4
28 weeks	2.42±0.28 ⁴⁾⁵⁾⁶⁾⁷⁾⁸⁾⁹⁾	10.51±1.60 ⁵⁾⁶⁾⁷⁾⁸⁾⁹⁾	2.45±0.24 ⁵⁾⁸⁾⁹⁾	10.68±3.05 ⁹⁾
29 weeks	2.54±0.29 ⁵⁾⁶⁾⁷⁾⁸⁾⁹⁾	10.71±1.65 ⁵⁾⁶⁾⁷⁾⁸⁾⁹⁾	2.71±0.24 ⁵⁾⁹⁾	11.13±1.82 ⁹⁾
30 weeks	2.96±0.36 ⁸⁾⁹⁾	13.18±3.12 ⁶⁾⁸⁾⁹⁾	3.12±0.12	13.36±1.51
31 weeks	3.15±0.62 ¹⁾	14.20±2.26 ⁹⁾	3.04±0.19	11.65±1.92 ⁹⁾
32 weeks	3.14±0.65 ¹⁾²⁾	14.84±2.55 ¹⁾²⁾⁹⁾	4.02±0.23 ¹⁾²⁾	15.58±1.77
33 weeks	3.35±0.50 ¹⁾²⁾	16.12±2.59 ¹⁾²⁾³⁾	3.38±0.26	12.93±2.56
34 weeks	3.19±0.50 ¹⁾²⁾	14.56±3.01 ¹⁾²⁾⁹⁾	3.48±0.20	13.20±2.51
35 weeks	3.47±0.40 ¹⁾²⁾³⁾	16.42±2.85 ¹⁾²⁾³⁾	3.79±0.27 ¹⁾	13.83±2.46
36 weeks	3.51±0.46 ¹⁾²⁾³⁾	17.57±2.86 ¹⁾²⁾³⁾⁴⁾⁵⁾⁷⁾	4.18±0.24 ¹⁾²⁾	16.02±2.35 ¹⁾²⁾⁴⁾

Two outliers were not included in the statistics. ¹⁾ compared with 28 weeks, $P<0.05$; ²⁾ compared with 29 weeks, $P<0.05$; ³⁾ compared with 30 weeks, $P<0.05$; ⁴⁾ compared with 31 weeks, $P<0.05$; ⁵⁾ compared with 32 weeks, $P<0.05$; ⁶⁾ compared with 33 weeks, $P<0.05$; ⁷⁾ compared with 34 weeks, $P<0.05$; ⁸⁾ compared with 35 weeks, $P<0.05$; ⁹⁾ compared with 36 weeks, $P<0.05$.

3 讨论

甲状腺产生的甲状腺原氨酸80%是四碘甲状腺原氨酸(T4),小于20%是三碘甲状腺原氨酸(T3),<1%为其他碘甲状腺原氨酸,包括反T3(RT3)和二碘甲状腺原氨酸(T2)。T4通过脱碘酶(deiodinase, D)的作用,转化为T3。在胎儿期,组织中T3浓度受到严格控制,T4更多转化为RT3,同时循环T3转化为T2失活^[6-8]。足月儿出生时,TSH迅速增加,刺激T3、T4分泌增加,24~36 h达到高峰^[7],1周左右逐渐下降,6个月时T4、FT4仍稍高于年长儿及成人^[3]。早产儿则不同,自出生至纠正胎龄足月,TSH变化平缓^[8];在32~33周的早产儿,生后1 h T3就开始升高,生后7 h T4才开始升高^[7],提示T3的增加,可能不在于甲状腺合成,而在于脱碘酶Ⅲ活性降低和脐带夹闭的影响。本研究中,TSH在3~7 d和8~21 d的比较无统计学差异,缺乏明显的TSH高峰,趋势平缓。3~21 d的FT4趋势与足月儿相仿,3~7 d较高,8~21 d则降低;FT3趋势则相反,3~7 d比8~21 d水平低。原因可能是:早产儿生后对甲状腺激素需求增加,以维持产热等生物过程;但HPT轴发育不成熟,出生时寒冷等因素未能刺激TSH相应增加;机体调节脱碘酶活性使T3降解减少,T4向T3转化增多,但甲状腺合成分泌T4、T3低下,故FT3升高缓慢,同时T4合成不足补偿转化的

消耗,逐渐下降。本研究中FT4在3~7 d随日龄增加而下降,在8~21 d则不受检查日龄影响,故推测T4向T3转化增多主要发生于生后1周内。FT3、FT4出生后的变化,不同胎龄的早产儿有所不同,如表7所示,在8~21 d,28~30周的FT4、FT3均较3~7 d时稍高,而31~36周的FT4较3~7 d降低时,FT3却较3~7 d升高,提示T4向T3的转化增多发生在较大胎龄早产儿,这与D2在妊娠晚期成熟是吻合的^[9]。

胎龄是影响3~7 d、8~21 d早产儿FT3、FT4的共同因素。胎龄越小,FT3、FT4水平越低,与甲状腺容积小、碘浓集与碘化甲状腺球蛋白能力低、硫酸盐化清除快、母亲TH供应中断、碘摄入不足或碘暴露增加^[7,10-11]等因素有关。本研究中,男性早产儿8~21 d的FT3、FT4较女性低。美国一项关于240万份新生儿CH筛查的研究^[12],发现男婴平均T4值和中位数T4值较女婴低,中位数TSH较女婴高。荷兰的一项4 237名儿童(中位年龄6岁,4.9~9.1岁)的研究^[13],男童比女童有更低的FT4和更高的TSH。从早产儿、足月儿到较大儿童,FT4在性别之间似乎存在天然的差异,原因并不十分明确。有研究发现GDM母亲的新生儿,脐血T4水平更高^[14],在本研究中没有类似改变,原因可能与本研究对象为早产儿,甲状腺不成熟,应激反应迟钝有关。采用辅助生殖技术的新生儿发生内分泌紊乱的机会增

加^[15],而本研究尚未发现其甲状腺功能与自然受孕者有明显差别。据报道双胎、多胎新生儿CH发病率比单胎高^[16]。本研究尚未发现双胎与单胎早产儿甲状腺水平的差别,这可能是样本量不足导致的。

本研究中胎龄不是TSH的影响因素,跟多数报道一致。也有研究认为胎龄影响早产儿TSH,甚至负相关^[8-9,17]。早产儿TSH可能与宫内“压力”性因素正相关,如阴道分娩、第二产程时间长、脐带绕颈、羊水胎粪污染、工具性分娩、低Apgar评分、男性性别等^[18]。值得注意的是,早产儿、低体质量儿TSH会延迟升高,多于2~6周发生,6~10周恢复。考虑到早产儿TSH分泌难以预测,故一次CH筛查可靠性比足月儿低,包括欧洲^[19]、日本^[20]及我国^[2,21]

的新生儿CH筛查指南建议对早产儿进行常规第2次筛查。

因此对于早产儿甲状腺功能检查,亟需建立一个胎龄相关的甲状腺激素参考范围,联合TSH、FT4或T4进行评估。

本研究仍存在诸多的局限。首先,209例病人中只有32例的第2次甲状腺功能检查纳入了统计,样本分布不均;其次各胎龄组的病例分布也不均匀,个别胎龄组样本量较小;母亲产前使用糖皮质激素也可能对新生儿的甲状腺功能产生影响。未来,可通过多中心联合扩大样本量、改善研究方法、延长随访的时间,以达到真正可以认识早产儿甲状腺的功能特征。

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(编辑 余菁)