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Association of Cord blood telomere biology with mother's education

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ABSTRACT

BACKGROUND:

Telomere, the biological chronometer, has been found to be influenced by different parameters which are reprogrammed during fetal life. This study was designed to find out influence of education on relative telomere length (RTL) of the maternal and new born and to detect improvement in the genetic remodeling during the fetal life between low and high educational levels of mother.

METHODS

Pregnant females(18-37 years) and their newborns (n=250) were recruited from Karachi hospitals. In this cross-sectional study RTL (maternal and cord) was calculated by Quantitative real-time PCR . Statistical analysis used were chi square tests and Mann Whitney U test for variables with two categories and then Kruskal Wallis for variables with more than two categories to examine mean difference between relative telomere length(RTL) and maternal education. The relationship between predictor variable(education) and RTL was done by linear regression.

RESULTS

A significant association of education and RTL revealed shorter mean maternal RTL(base pair(bp)) 6380±1128 among females with low education and longer 6553±945 in high education females respectively (p=0.071) (B= 0.009 p = >0.05). Similarly, cord RTL were shorter 6600±1218 in low and longer 7154±1585 in high education group(p=0.007)(B= 0.184 p = <0.05) at 95% confidence level. It was also found that newborn among high education with upper middle Socioeconomic status (SES) have significantly longest RTL 7262±1804(p =<0.05).

CONCLUSION

Overall longer newborn RTL than mothers were observed among different levels of education in targeted population of Karachi where higher education have a shielding effect on telomere remodeling during the fetal development.

Keywords: Telomere; Education; Socioeconomic status(SES); Remodeling

INTRODUCTION

Genomic instability of chromosomes is very much dependent on ribonucleoprotein complexes at the end of chromosomes called telomeres. They protect chromosomes from catastrophic events of degradation or interchromosmal fusion with another telomere or with a broken DNA end. Because of its shape and function it is related to the plastic caps on shoelaces [1]. Telomeres are long non-coding tandem repeat sequences (TTAGGG) with 3' G-rich single stranded extension of 200bp at the end of chromosomes. These repeats varies per chromosome from 20 bps to many kilo bps among different individuals. At birth telomeres are longest with size 7 to 20 kb [2] but sometimes it become highly variable [3]. In newborn girls they are longer by 6.83% or 50-100bp greater than boys [4].

Intrauterine period of life is most sensitive period of fetal cell proliferation, maturation, differentiation and drastic respond to external or internal environmental factors. Fetus development is susceptible to various influences, mainly affected via maternal tissues. Epigenetic such as maternal exposed environment, physical activity, education, [5] mental and physical status, can disturb the health and phenotype of the growing child by genetic programming of fetus. Endocrine disorders during pregnancy, toxins, infectious agents, maternal nourishment status and placental functionality can prompt fetal gene expression modifications [6]. Fetal programming is a critical period of intrauterine life due to the disruption of normal development by certain factors which can cause adaptive changes in growth and development of fetus. Similarly, a research was done to check an effect of exposome at molecular level and they found its role in alteration in DNA, protein and lipids. Such series of cascade reactions may lead to new altered genetics which can result in adverse outcomes [7]. Current knowledge unambiguously emphasizes the fact that the intrauterine environment to which a fetus is exposed can have a long-term impact on health after birth and generations after generations [8].

The association of telomere with education, ethnicity and socioeconomic status causes increase in oxidative stress and inflammation leading to morbidity and mortality [9, 5]. A Whitehall study on British civil servants found that lower educational attainment was associated with shorter telomeres but income and occupational grade had no significant results [10]. Multiple studies have reported that low education have their long term effects on telomere, acting as biological age predictor [11-13].

The purpose of this study was to determine the association of telomeres with maternal education in Pakistani population. Thus, research can be novel and informative work which can fill the gap of knowledge regarding telomeres in target population. This study was designed to find out influence of low and high educational levels of mother on telomere remodeling during the fetal life.

METHODS

A total of 250 pregnant females(18-37 years) were recruited at the time of delivery with their newborns from Ziauddin Medical Hospitals, Karachi between May 2018 to Oct, 2018. This is a cross sectional study

and blood samples were collected after approval from Ethics Review Committee (ERC) of Ziauddin University and Hospital. Pregnant females with known malignancies or any cancer and with known diabetes mellitus were not included in the study. Females were distributed into low(no education, less than high school, high school) and high(graduation, university) educational groups[14] using consecutive sampling technique. Socioeconomic status(SES) was defined using family income per month Low: <15000, lower middle: 16000-25000, upper middle: 26000-100,000 and high: < 100,000.($ rate October, 2018)[15]. After taking the informed Consent, questionnaire was filled from patient or their attendants' and rest of the information was taken from hospital records. Venous blood (3-5 ml) samples of pregnant female were collected in ethylenediaminetetraacetic acid (EDTA) tubes before delivery. Umbilical cord blood (3-5 ml) samples were collected immediately postpartum into EDTA tubes from the cord when it was still in contact with maternal placenta. Samples were then transported to laboratory and stored at -20°C. DNA EZ-10 spin column genomic DNA kit (BioBasic Canada inc.) was used for DNA extraction. Gradient SimpliAmp conventional thermal cycler (Applied Biosystem) was used to optimize temperature. Then quantitative analysis was done by real time PCR by using kit method (Platinum SYBR Green qPCR SuperMix-UDG, Invitrogen). Primer sequences for telomere and reference single-copy gene (β *globin*) amplification were:

Tel F, 5'GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT 3';**Tel R**, 5'TCCCGACTATCCCT ATCCCTATCCCTATCCCTATCCCTA 3'; **HBG F**,5'GCTTCTGACACAACTGTGTTCACTAGC 3'; **HBG R**, 5'CACCAACTTCATCCACGTTCACC 3' [16]. Electrophoresis was done on 2% agarose gel by using 50 base pair (bp) DNA ladder (invitrogen). For qPCR 30 µl reaction mixture (15µl of master mix, 2.5 µl of 10uM forward primers, 2.5 µl 10uM reverse primers, 1 µl ROX dye and 10 µl DNA(1-6 ng)) was prepared for analysis. Temperatures for telomere PCR: first holding stage for 50 ℃ for 2 min and 95 ℃ for 2 min, then 40 cycles were set at denaturation 95℃ for 15 sec, annealing at 68℃ for 40 sec and extension 75℃ for 3 min and second holding for 72 ℃ for 40 sec. Temperature for reference single-copy gene (β *globin*) PCR: first holding stage for 50 ℃ for 2 min and 95 ℃ for 2 min, then 40 cycles were set at denaturation 95℃ for 15 sec, annealing at 56℃ for 40 sec and extension 75℃ for 3 min and second holding for 72 ℃ for 40 sec. The ct(cycle threshold) was measured by Step one software(v2.3) to calculate relative telomere length of maternal and cord blood samples. Telomere/ single gene copy (T/S) ratio was determined and for lowest variability, triplicate measures for the DNA samples were performed [16]. T/S ratio was then converted to base pairs (bp) by using formula.

(3,274 + 2,413 * (T/S)) [9]

STATISTICAL ANALYSIS: Statistical package for social sciences (SPSS) version 20 was used for analysis of data. Quantitative variables considered in study were presented by Mean± SD and qualitative variables were presented by frequency and percentages. At 95% confidence level tests applied were chi square and Mann Whitney U for variables with two categories and then Kruskal Wallis for variables with

more than two categories to examine mean difference between maternal and cord blood relative telomere length(RTL). The relationship between education and RTL was done by linear regression.

RESULT

The data of this study was divided into two major educational groups: low education n=174(69.6%) and high education n=76(30.4%) (Table 1). The most frequent maternal age range among low group was (23-27), n=60(34%) and in high group (28-32), n= 33(43.3%) having significant *p*=<0.05.

Telomere PCR electrophoresis was visualized in UV trans illuminator(figure 1a).The real time PCR ct values for telomere and reference gene (figure 1b) was used to calculate the mean maternal RTL of low education group 6380±1128 and high education group 6553±945 *p*=0.071(B= 0.009 *p* = >0.05). Whereas the mean cord RTL of low and high education was 6600±1218, 7154±1585 had significant association *p*=0.007(B= 0.184 *p* = <0.05) (figure 2, Table 1).

Table 1: Selected characteristics of pregnant women and newborns

Variables	**Low education n=174(69.6 %)**		**High Education n=76(30.4%)**		***p*-value**
	n	%	N	%	
Maternal Age(years)					
18-22	42	24.1	6	7.9	<0.05
23-27	60	34.5	23	30.3	
28-32	44	25.3	33	43.4	
33-37	26	14.9	14	18.4	
Socioeconomic status (SES)					
Low	63	36.2	-	-	0.999
Lower middle	60	34.5	3	3.9	
Upper middle	43	24.7	19	25.0	
High	8	4.6	54	71.1	
Newborn gender					
Girl	88	50.6	45	59.2	0.312
Boy	86	49.4	31	40.8	

Newborn weight (kg)					
2.0-2.5	90	51.7	37	48.6	<0.05
2.6-3.0	59	33.9	29	38.2	
3.1-3.5	17	9.8	8	10.5	
Newborn gestational age(weeks)					
36-38	88	50.6	35	46.1	<0.05
39-41	82	47.1	40	52.6	
Maternal Relative telomere length(bp) (Mean± SD)	6380±1128		6553±945		0.071
Cord relative telomere length(bp) (Mean± SD)	6600±1218		7154±1585		0.007

Chi square and Mann Whitney U test was used to determine the comparison of different variables among low and high educational groups.

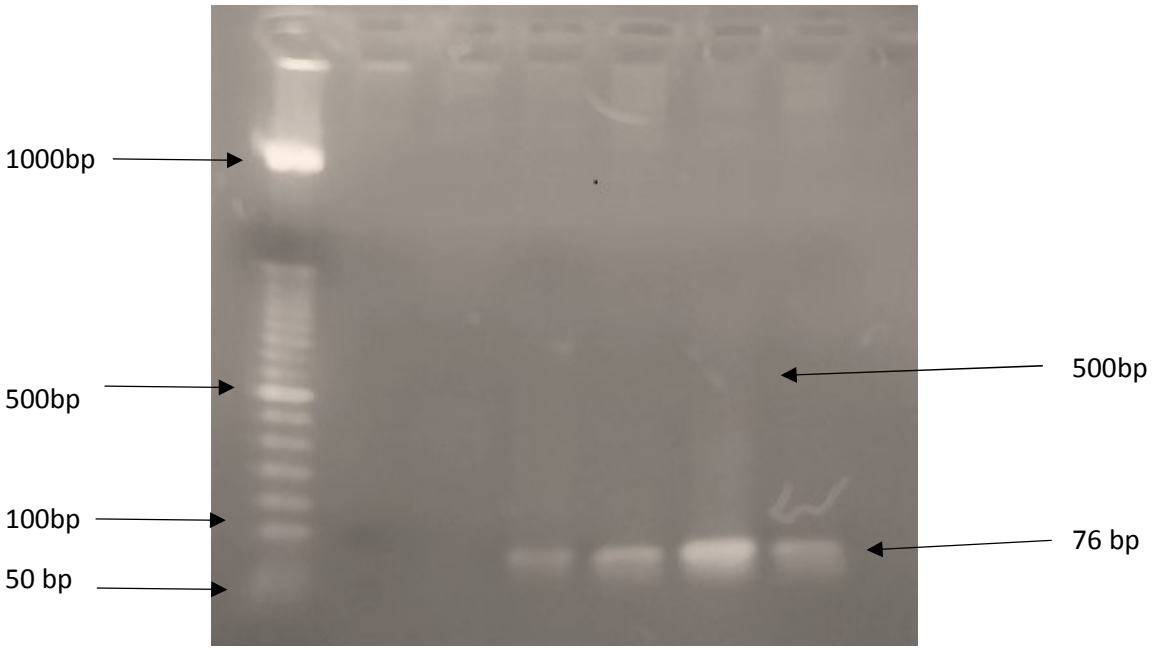

Figure 1a: Agarose gel electrophoresis of conventional PCR analysis of DNA samples.

Lane L: 50 bp ladder(Invitrogen) , lane 1-7: DNA samples

Lane 3-6: 76 bp smallest telomeres product and fading to background at ~500 bp.

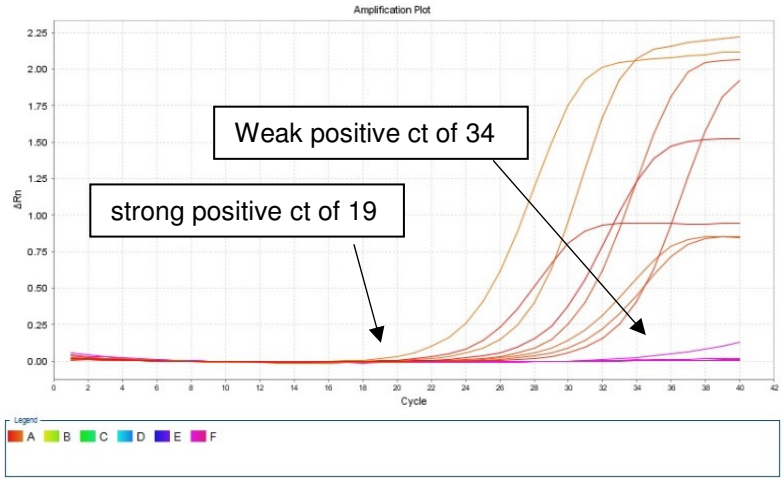

Figure 1b: Real time PCR analysis of DNA samples after optimization by conventional PCR.

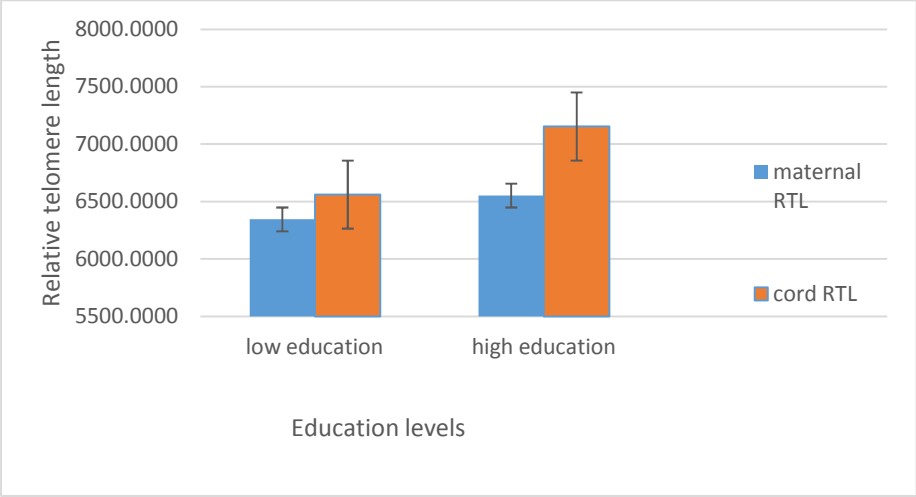

Figure 2: Relative telomere length (RTL) between low and high educational groups.

In our study mostly females of low education group belongs to low SES n=63(36%) and only few were from high SES n=8(4.6%). Whereas in high education group females from high SES n=54(71%) had high frequency but lower middle SES females n=3(4%) were also seen (Table 1). On comparison of maternal RTL between both educational groups, we found shortest RTL 5892±755 in low education group with low SES and longest RTL 6714± 1283 was also seen in low education with high SES(p =<0.05). Whereas, longest cord(newborns) RTL was revealed in both low and high education group of upper middle SES 7262±1804, 7977±2019 with significant results (p =<0.05) (Table 2).

There was almost equal newborn gender in low educational group n=88(50%), n=86(49%) with average newborn weight between 2.0-2.5 kilogram(kg). Whereas high educational group had more newborn girls n=45(59%) than boys n=31(41%). Majority of the newborn girls have longer RTL 6615±1256, 7159±1613 than boys with statistically no significance (p= >0.05) (Table 2). Surprisingly RTL 7042±1596 of newborn having weight between 2-2.5 kg in high education group was longest among all the telomere lengths in newborns. Gestational age of newborn above 39 weeks was seen most frequently in both educational groups (n=82(47%), n= 40(52.6%)) (Table 1). In our study we have perceived that large gestational age newborns have longer RTL in both groups of education. Longest RTL 7349±1481 was seen in high educational group newborns with 36-38 week gestational age (p=0.322), whereas there was decrease in maternal RTL with increase in gestational weeks. (Table 2).

Table 2: Mean difference of maternal and cord RTL of different variables in low and high education groups.

Variables	Maternal Relative telomere length(bp)		Cord Relative telomere length(bp)	
	Low education	High Education	Low education	High Education
Maternal Age(years)				
18-22	6162 ±1150	6717±1033	6242± 802	6717±877
23-27	6623 ±1197	6645±890	6697 ±1363	7447±2031
28-32	6291± 920	6629±1063	6638 ±993	6998±1209
33-37	6131 ±1089	6182±667	6779 ±1643	7270±1878
***P*-value**	**0.58**	**0.352**	**0.401**	**0.873**
Socioeconomic status (SES)				
Low	5892±755	-	6190±620	-
Lower middle	6471±1069	6044±711	6502±955	6504±477
Upper middle	6801±1349	6685±847	7262±1804	7977±2019
High	6714± 1283	6539±989	6940±1337	6977±1333
***p*-value**	<0.05	0.419	0.004	0.009
Newborn gender				
Girl	6436±1199	6536±1116	6615±1256	7159±1613
Boy	6272±1023	6576±662	6559±1188	7147±1573
***p*-value**	0.532	0.653	0.845	0.986
Newborn weight in kilograms(kg)				
2.0-2.5	6549±1314	6452±931	6717±1352	7042±1596
2.6-3.0	6181±917	6670±1093	6469±1108	6907±1212
3.1-3.5	6185±993	6796±627	6526±1404	6790±849
***p*-value**	0.520	0.956	0.730	0.322
Newborn gestational age(weeks)				
36-38	6337±1226	6592±851	6456±1318	7349±1481
39-42	6341±1019	6564±1026	6726±1130	6954±1694
***p*-value**	0.772	0.339	0.075	0.097

P-value was calculated by Krushkal Wallis and Mann Whitney to examine the differences of RTL between subgroups.

DISCUSSION

The current study confirms the effect of education on the RTL of mother and can carry over to their newborns. Precisely, lower education with low SES was found associated with shorter telomere length. In consistent with our study there are many studies that reinforced our hypothesis of mother's education and intellectual ability's strong impact on telomere attrition [17-20]. A data from a health Survey reported significantly shorter telomeres (5.49 kb) in a high school adults as compared to the graduated adults (5.63 kb) ($p< .01$)[9,21]. In the this study we also observed shorter RTL (6380bp, 6600bp) in both maternal and cord blood of low educational group compared to high educational group (6553bp,7154bp)(p=0.007)(figure 2). Whereas, there was 173bp increase in newborn of low education females and 554bp increase in high education group. The length difference between two groups signifies the more telomere remodeling during fetal development in high education females. Thus, increase of telomerase enzyme during fertilization can also be responsible for fetal telomere biology [22]. Varying increase in cord telomere length between educational groups may determines health status of newborn due to fetal telomere programming [23]. So, females with less education during perinatal period and family social support with lower values could lead to shorter telomeres with distinct risk factors for cellular aging and disease incidence. A study by Mitchell was also in accordance with our study findings and established association of mothers education (high school and college) with telomeres, thus longer telomere length was observed in college graduates (p= 0.001) [24]. Another study conducted in different universities of US (6.3kb(university of Texas), 6.4 kb(university of pennsylvania), 8.7 kb(Ohio state university) marked the strong relationship of education and telomere length [18].

In different studies no association was observed, where education was not properly measured as key feature or other factors had vital role during the RTL analysis [25,26].

SES have a potential to cause the genomic instability by increase in oxidative stress and health disparities due to physical, mental, and behavioral insults. In our study we observed shortest RTL in both females and their newborns having low education with low SES and longer RTL in maternal and cord RTL of high or upper middle SES with high education. A study by Alder also supported our results having association between telomere, education and sociodemographic characteristics, signifies females attending high school had longer telomeres than those with less than high school education (4926 versus 4806 base pairs). [27]

Aging is the process that started before birth and leads to cellular senescence. Previous study had reported 25 % decrease in RTL in placenta tissues during the third trimester of gestation which was opposite to our study observations [28]. In this respective study we revealed increase in telomeres length (6456-7349) with large gestational age in newborns, nevertheless, there was no significant mean

difference seen among different gestational ages (p= 0.075,0.097). No study was found till date which observed the direct association of education and gestational age.

In a study an increase in birth weight percentile with longer telomere (p=0.048) was witnessed in females getting education beyond high school. These females have ~500bp increase in telomere length in newborns than low education females [29]. In our study we did not noted the increase in telomeres with increase in newborn birth weight among both low and high education females (p= 0.322). Similar to current study it was also found no significant differences in newborn telomere with maternal education among newborns birth weight [30]. We also illustrated that in high educational group females newborn gender was mostly girls with longer RTL [4, 31].On Contrary a study reported 34% of the variance in telomere length in male gender and found association of telomere length with higher maternal educational, income and emotional health during pregnancy [32].

Our study add data to the growing literature and research on education of mothers and newborn telomere length and may act as risk factor causing cellular aging and health disparities. This study clearly emphasizes on the fact that the intrauterine environment may have an impact on genetics and can transmit generations after generations. Moreover, the relationship between RTL and maternal education had been assessed for the first time in Karachi population to highlight improvement in the genetic remodeling during fetal life.

CONCLUSIONS

This study identified the association between maternal education and telomere biology in Pakistani females-newborns and their role in morbidity and mortality. Our finding revealed low education with shorter RTL both in maternal and cord compared to higher education. Overall longer newborn RTL than mothers were observed among different levels of education in targeted population of Karachi.

LIMITATIONS

In our study small sample size and financial constraints were major limitations. We were not able to take information about father and family, which could be important for the detection of inheritance pattern of telomeres. Further investigations on maternal parameters could also be helpful in revising the data.

FUTURE RECOMMENDATION

Longitudinal cohort studies can be done to monitor patients around the diverse factors like physical exercise, diet, sleep, environmental pollution that can influence the size of the telomeres and evaluation of telomerase level in the blood. Southern blotting should be done to validate the results.

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CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

INFORMED CONSENT: Informed consent was obtained from all individual participants or their attendant's included in the study

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