The association of Cord blood telomere biology with mother's education

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

Quantitative real-time PCR method was used to analyze maternal and cord RTL's between mother-newborn (n=250) from a Karachi population. In this study we used 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 relationships between relative telomere length(RTL) and maternal education. The relationship between predictor variable and RTL was done by linear regression.

RESULTS

The females were divided into low education n=174(69.6%) and high education group n=76(30.4%) having mean maternal RTL in base pair(bp) 6380±1128, 6553±945(p=0.071) (B= 0.009 p = >0.05) respectively. Comparatively, cord RTL were shorter 6600±1218 for low and 7154±1585 for high education (p=0.007) (B= 0.184 p = <0.05) at 95% confidence level. Smallest RTL 5892±755 were among low socioeconomic status (SES) with low education. Cord (newborns) of high SES with high education had longest RTL 7262±1804 (p =<0.05). Larger gestational age showed longer newborn RTL, both in low and high educational groups (p=0.097).

CONCLUSION

Overall longer newborn RTL than mothers were observed among different levels of education in targeted population of Karachi (p=<0.05). However, low education revealed shorter RTL both in maternal and cord compared to higher education.

Keywords: Education; Telomere; Gestational age; Socioeconomic status(SES)

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 of 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 on molecular level and found its damage to DNA, protein and lipids. Such series of cascade reactions may leads 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 [11,12,13].

The purpose of this article was to review the current state of knowledge regarding telomeres and its association maternal education in Pakistani population. Thus research can be novel and informative work which can fill the gap of knowledge and help in risk prediction for different diseases in target population. This study was designed to find out influence of education on 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

The study includes 250 pregnant females(18-35 years) and their newborns from Ziauddin Medical Hospital, Karachi. The study is a cross sectional study and samples were collected after approval from Ethics Review

Committee (ERC) of Ziauddin University and Hospital. Samples were distributed into low(no education, less than high school, high school) and high(graduation, university) educational groups. SES with defined income per month ($ rate October, 2018). Low: <15000, lower middle: 16000-25000, upper middle: 26000-100,000 and high: < 100,000 (world bank, 2018). 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 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' [14]. 2% agarose gel was used for electrophoresis analysis. 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 and10 µl DNA(1-6 ng)) was prepared for analysis. Temperatures for telomere PCR: first holding stage for 50 °C for 2 min and 95 °C for 2 min, then 40 cycles were set at denaturation 95°C for 15 sec, annealing at 68°C for 40 sec and extension 75°C for 3 min and second holding for 72 °C for 40 sec. Temperature for β *globin* reference gene PCR: first holding stage for 50 °C for 2 min and 95 °C for 2 min, then 40 cycles were set at denaturation 95°C for 15 sec, annealing at 56°C for 40 sec and extension 75°C for 3 min and second holding for 72 °C for 40 sec. The ct(cycle threshold) values by Step one software(v2.3) was used to measure relative telomere length of maternal and cord blood samples and then telomere/ single gene copy (T/S) ratio was calculated [14]. 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 predictor variable and RTL was done by linear regression.

RESULT

The data of this study was divided into two major educational groups: low education(no education, less than high school, high school) n=174(69.6%) and high education(graduation, university) n=76(30.4%) (Table 1). The most frequent maternal age range among both groups was (23-27), n=60(34%) in low and (28-32), n= 33(43.3%) in high group having significant *p*=<0.05.

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					<0.05
18-22	42	24.1	6	7.9	
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)					0.999
Low	63	36.2	N/A	N/A	
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					0.312
Girl	88	50.6	45	59.2	
Boy	86	49.4	31	40.8	
Newborn weight (kg)					<0.05
1.5-2.00	19	10.9	9	11.8	
2.1-2.5	71	40.8	28	36.8	
2.6-3.0	59	33.9	29	38.2	
3.1-3.5	17	9.8	8	10.5	
Newborn gestational age(weeks)					<0.05
33-35	11	6.3	N/A	N/A	
36-38	77	44.3	35	46.1	

39-42	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

N/A: Data not available, Chi square and Mann Whitney u test was used to determine the difference between educational groups.

The mean relative telomere length was calculated from T/S ratio formula which converted RTL into base pairs by multiplying with reference DNA telomere length, 4,270bp [9]. The mean maternal RTL of low education group was 6380±1128 and high education group was 6553±945 with no statistically significance *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 statistically significant relationship *p*=0.007(B= 0.184 *p* = <0.05) (fig 1, Table 1).

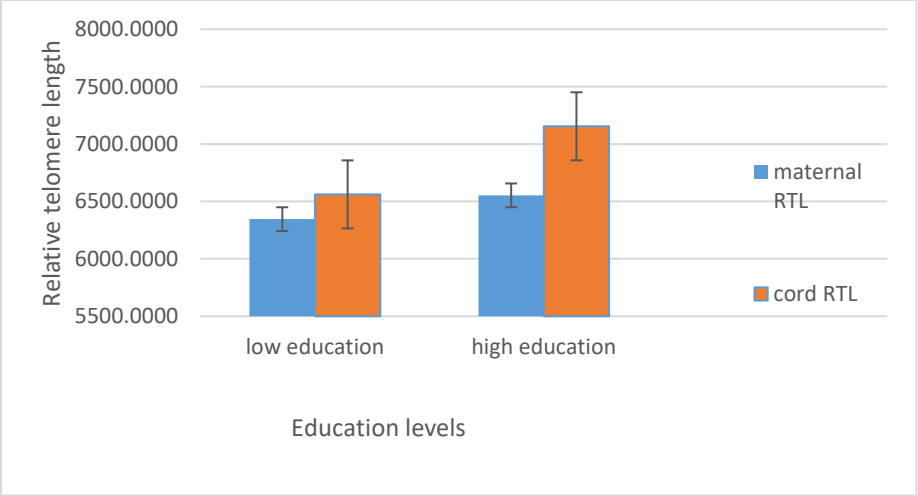

Figure 1: Relative telomere length (RTL) between low and high educational groups.

In our study mostly females of low education group belongs to low SES n=63(36%) and n=8(4.6%) were from high SES. Whereas in high education group females from high SES n=54(71%) had high frequency and n=3(4%) lower middle SES females were also seen (Table 1). Mean difference between the different SES with low education had revealed lowest RTL 5892±755 in mothers of low SES and longest RTL 7262±1804 in cord(newborns) of high SES with significant *p* =<0.05(fig 2, Table 2). Analysis of high education group marked upper middle SES had longest RTL 6685±847, 7977±2019 in both mother and cord *p* =0.419, 0.009 whereas low SES mother had smallest RTL 6044±711(fig 2,Table 2).

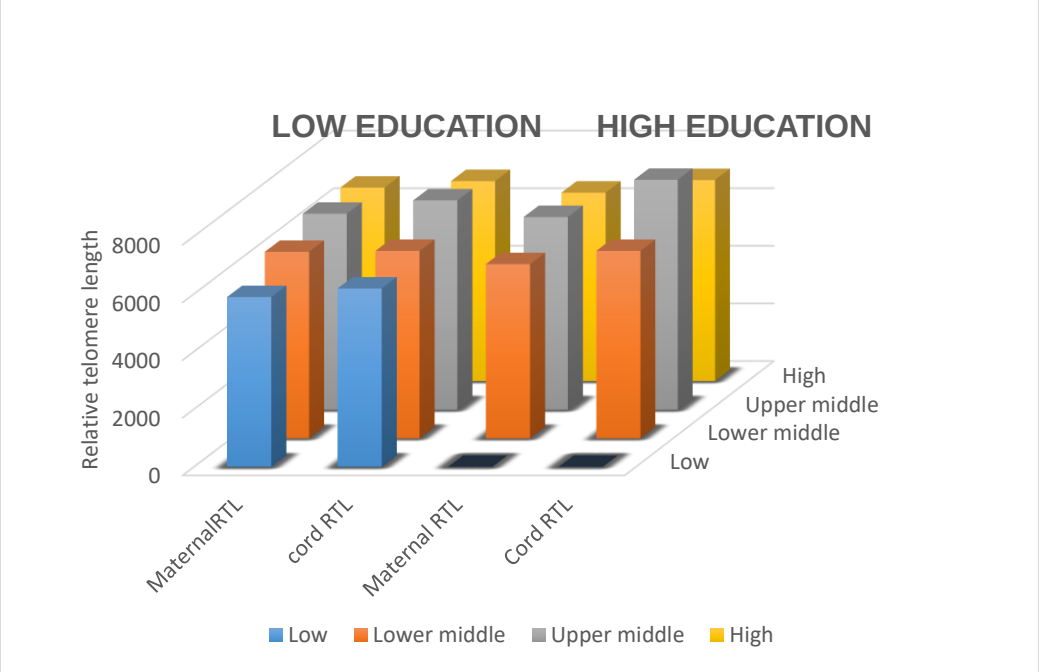

Figure 2: Maternal and cord RTL between different SES with low and high education group

There were almost equal newborn gender in low educational group n=88(50%), n=86(49%) with average weight between 2-2.5 kilogram(kg). Whereas high educational group had more newborn girls n=45(59%) with average weight of the 2.5-3.0kilogram (kg). All 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 between mother-newborn variables among low and high educational group

	LOW EDUCATION N=174(69.6 %)		**HIGH EDUCATION N=76(30.4%)**	
VARIABLES	Maternal Relative telomere length(bp)	Cord Relative telomere length(bp)	Maternal Relative telomere length(bp)	Cord Relative telomere length(bp)
MATERNAL AGE				
18-22	6162 ±1150	6242± 802	6717±1033	6717±877
23-27	6623 ±1197	6697 ±1363	6645±890	7447±2031
28-32	6291± 920	6638 ±993	6629±1063	6998±1209
33-37	6131 ±1089	6779 ±1643	6182±667	7270±1878
***P*-VALUE**	0.58	0.401	0.352	0.873
SOCIOECONOMIC STATUS(SES)				
LOW	5892±755	6190±620	N/A	N/A
LOWER MIDDLE	6471±1069	6502±955	6044±711	6504±477
UPPER MIDDLE	6801±1349	7262±1804	6685±847	7977±2019
HIGH	6714± 1283	6940±1337	6539±989	6977±1333
***P*-VALUE**	<0.005	0.004	0.419	0.009
NEWBORN GENDER				
GIRL	6436±1199	6615±1256	6536±1116	7159±1613
BOY	6272±1023	6559±1188	6576±662	7147±1573
***P*-VALUE**	0.532	0.845	0.653	0.986
NEWBORN WEIGHT IN KILOGRAMS(KG)				
1.5-2.00	6302±874	6517±800	6471±625	8605±2560
2.1-2.5	6549±1314	6717±1352	6452±931	7042±1596
2.6-3.0	6181±917	6469±1108	6670±1093	6907±1212
3.1-3.5	6185±993	6526±1404	6796±627	6790±849
***P*-VALUE**	0.520	0.730	0.956	0.322

NEWBORN GESTATIONAL AGE(WEEKS)				
33-35	6689±966	6339±1029	N/A	N/A
36-38	6337±1226	6456±1318	6592±851	7349±1481
39-42	6341±1019	6726±1130	6564±1026	6954±1694
***P*-VALUE**	0.772	0.075	0.339	0.097

N/A: Data not available. *P* value was calculated by Krushkal Wallis and Mann Whitney to examine the differences of RTL between subgroups.

DISCUSSION

The current study confirm the effect of education and socioeconomic status(SES) on the relative telomere length(RTL) of mother can carry over to their newborns. Precisely, lower education and 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 strong impact on telomere attrition [15,16,17,18]. A data from a health Survey reported significantly shorter telomeres 5.49 kb in a high school adults as compared to the graduated adults having longer telomere length 5.63 kb ($p< .01$)[9,19]. In the this study we also observed shorter RTL 6380, 6600 in both maternal and cord blood of low educational group as compared to high educational group females 6553,7154(p=0.007)(fig 1). Therefore there was 173 base pair (bp) increase in newborn of low education females and 554 base pair(bp) 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 [21]. Varying increase in cord telomere length between educational groups may determines health status of newborn due to fetal telomere programming [20]. So females with less educational 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 two educational groups(high school and college) of mothers with longer telomere length in college graduates (p= 0.001) [22].

Another study conducted in different universities of US marked the strong relationship of education and telomere length: 6.3kb(university of texas, 6.4 kb(university of pennsylvania), 8.7 kb(Ohio state university)[16]. No associations was observed in studies in which education was not properly measured as key feature or other factors had vital role during the RTL analysis [23,24].

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 females having low SES with low education had smallest RTL 5892±755 as compared to females of high SES with high education. Longest RTL was seen in newborns of upper middle SES 7977±2019 (p=0.009). Thus we comprehend that high SES with high education had longer RTL than low SES with low 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 a high school education or less (4926 versus 4806 base pairs). [25]

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 [26]. In this respective study we have comprehended increase in telomeres length (6339-7349) with large gestational age in newborns, nevertheless, there was no significant mean difference seen among different gestational ages (p= 0.075,0.097). Opposite result to our study reported longer telomeres in preterm than large gestational age(LGA) babies [27]. No study was found till date which observed the direct association of education and gestational age.

Increasing birth weight percentile with longer telomere (P=0.048) was witnessed in female getting education beyond high school. These female have ~500 base pairs increase in telomere length than low education [28]. In our study we did not noted the longer telomeres with increase in newborn birth weight among both low and high education females.(p= 0.322). Similar to current study it was found elsewhere no significant differences in newborn telomere with maternal education among low birth weight newborns [29]. We also illustrated that in high educational group females newborn gender was mostly girls with longer RTL [4, 29]. 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 [30].

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 a long-term impact on health after birth and 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

Relative telomere length (base pair) of maternal and cord blood was calculated by Quantitative PCR. 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 RECOMMENDATIONS

Longitudinal cohort studies should be done to monitor all the risk factors and evaluating the 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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