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PARENTAL DEMOGRAPHIC RISK FACTORS OF PRETERM BIRTH IN PAKISTAN: CASE CONTROL STUDY

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Abstract:
*Objective: To explore demographic risk factors for preterm birth in Pakistan. **Methodology:** This case control study was designed at Hajvery University by taking data from Obstetric and Gynecology department of different hospitals of 4 provinces, in Pakistan. The study was the study was completed in ten months i.e. Oct 2016 till September 2017. A total of 1098 i.e. 364 preterm birth (cases) and more than double i.e. 734 full term babies (controls) were taken in this study. **Results:** The mean age of mothers in preterm and full term group were 31.33 ± 8.12 years and 29.29 ± 6.17 years, respectively. The mean ages of mothers at time of marriage in preterm and full term group were 22.01 ± 5.92 years and 21.75 ± 4.98 years, respectively. Whereas, mean father's age in preterm and full term group was 35.15 ± 8.66 years and 32.80 ± 7.12 years and mean age of father's at the time of marriage was 26.59 ± 6.30 years (in preterm group) and 26.01 ± 5.74 years (in full term group). According to adjusted odds ratio in final model of current study the higher contributor of PTB among demographical variables were, mother's age ≥ 35 , mother's age ≤18, father's age ≥ 35, parent's marriage <20 years as a predictors of PTB. **Conclusion:** Through the findings of current study it is concluded that mother's, father's and combined (parent's) lower and advanced age is a major contributor of preterm birth in Pakistan. Even though unadjusted analysis their marriage in teen can also leads to preterm birth. Though in this article only demographic analysis is done and many other related factors were not included. So, further studies are needed to explore further factors as well.*

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Please cite this article in press Asif Hanif et al., ***Parental Demographic Risk Factors of Preterm Birth in Pakistan: Case Control Study .,*** *Indo Am. J. P. Sci, 2018; 05(10).*

INTRODUCTION:

Preterm birth (PTB) defined as delivery of a baby before 37 completed weeks of gestation, is associated with complications that lead to one million child deaths annually among neonates.[1]

It is also associated with increased risk of post neonatal mortality and morbidity.[2] PTB is an important perinatal health problem across the globe especially in developing countries. [3] The exact burden of PTB high and is keep increasing in regions with reliable reported and published data.[4]

A better understanding of the causes of preterm birth and exact estimates of the burden of PTB at global level are needed to opt preventative strategies to reduce PTB and to cope with its risk factors.[3] From the past few years, a growing trend has been noticed in the advanced maternal age. If the age of mother is 35 years or more, then this is considered as advanced age [5]. Adverse pregnancy outcomes are significantly associated with advanced maternal age thus these pregnancies are regarded as high risk [6, 7]. Several women intentionally postpone their pregnancy even up to the age of 40 due to various reasons, like career, educational and financial [8]. Teenage mothers (<20 years) also possess an augmented risk of poor fetomaternal outcomes and also have high risk of preterm delivery as compared to mothers of age 20 to 39 years old. The rate of extreme prematurity among teenage mothers is also very high [9]. The teenage mothers are predisposed to subclinical infection due to immaturity of uterine or cervical blood supply and there is also raise in production of prostaglandin production, which consequently higher their risk of preterm delivery. Many teenage mothers compete with the growing fetus for nutrients as they also fall in the growing age which results into fetal demise. This assumption is reinforced by evidence that increment in the weight during pregnancy is far more serious for a teenage mothers as compared to older mothers [10]. The odd ratio for advanced maternal age is reported from 1.04 [11] to 2.4 [12] showing significantly higher risk of PTB for advanced maternal age. For lower age group the risk of PTB is reported from 1.11 times to 3.4 times in literature [13], [14]. As for as father age is concerned it is evident that average paternal age is increasing due to various reasons and this health issue is not publicly projected or discussed. Increase in the risk in particular conditions among older fathers can be due to accumulated chromosomal aberrations and mutations taken place in the course of maturation of male germ cells. Latest's researches have also showed that fertility is decreased and incidence of birth defect is increased in the offspring of older fathers [15]. For advanced father's age few studies are available with different study designs but larger sample size were taken.[16-18].

There is no detailed study on Pakistan population regarding risk factors of PTB. The current study was designed to study the parental (both mother and father) demographical, epically age related risk factor of preterm birth in Pakistan. As there was no literature available considering factors of both mother and father in local population. In Past the major focus is always put on mother's factor but in this study it was proposed that father's demographic factors may also play important role in occurrence of PTB.

MATERIALS AND METHODS:

This case control study design at Hajvery University where a list of hospitals having Gynecology department of 4 provinces was made and then using lottery method (a random process) permission request was sent for data collection. Data from 4 different hospitals of four provinces of Pakistan was collected, i.e. Lady Aitchison Hospital, Lahore (Punjab Province), Bacha Khan Medical College, Mardan, (Khyber Pakhtunkhwa Province), Civil Hospital Quetta (Baluchistan province) and department of Obs and Gyne of Liaquat University of Medical & Health Sciences (Sindh Province). Non-probability convenience sampling was used. The study was the study was completed in ten months i.e. Oct 2016 till September 2017. A total of 1098 i.e. 364 preterm birth and more than double i.e. 734 full term babies were taken in this study. For controls (full term birth), all females delivering baby at 37 - 41 weeks of gestation (on dating scan) and for cases (preterm birth) all females regales of age and parity delivering baby before 37 weeks of gestation (on dating scan) were taken. Unwilling females to participate in the study , termination of pregnancy before 26 weeks of gestation , females with unconfirmed gestational age and females with short cervix were excluded from the study.

Finally data was collected from hospitals who gave the written permission. All data collection was based on predefined inclusion and exclusion criteria. The included females were divided into two groups i.e. PTB (delivery < 37 weeks) and FTB (≥ 37 -41 weeks) at time of birth. All pregnant women hospitalized after delivery in selected hospitals were taken after taking written informed consent in English as well as in Urdu. Females after 24 hours of delivery were approached with the help of consultant, duty doctor or duty staff nurse to collect related data.

Current age of mother (years), age of mother at marriage (years), current age of father (years) and age of father at marriage (years) were noted then these ages were categorized as ≤ 18 years and ≥ 35 years, moreover their age at time of marriage was categorized as < 20 years (teen age marriages). Data was entered and analyzed using SPSS version 22. For descriptive presentation of data mean ± S.D was used for quantitative data and frequency (%) was used for qualitative data. Chi-square test and unadjusted odd ration was applied for 2 x 2 tables. Forward conditional Logistic regression was applied to make the final model of parental demographic risk factors for preterm birth. OR>1 and *p-value* <0.05 were considered as significant.

RESULTS:

The mean ages of mothers in preterm and full term group were 31.33 ± 8.12 years and 29.29 ± 6.17 years, respectively. The mean ages of mothers at time of marriage in preterm and full term group were 22.01 ± 5.92 years and 21.75 ± 4.98 years, respectively. Whereas, mean father's age in preterm and full term group was 35.15 ± 8.66 years and 32.80 ± 7.12 years and mean age of father's at the time of marriage was 26.59 ± 6.30 years (in preterm group) and 26.01 ± 5.74 years (in full term group). The mean age of mother and father was statistically higher in preterm birth groups, p-value < 0.001 while there was no difference in mean ages of mothers and fathers at time of their marriage in PTB and FTB, *p-value* >0.05. Age of mother, father and combined for both parents was divided into lower age (≤ 18), advanced age (≥ 35 years) and their marriage in teen age group was also taken as risk factor. So, in PTB group there were 20 (5.5%) females who had age ≤ 18 and 344 (94.5%) females were > 18 years old. In FTB group there were 18 (2.5%) females with age of ≤ 18 years and 716 (97.5%) were > 18 years old. There was significant association between age and preterm birth

and there was 2.13 times higher chances of PTB in females having age ≤ 18 years i.e. OR = 2.13 (1.208, 4.428). There were 158 (43.4%) cases whose age was ≥ 35 years and 206(56.6%) cases had age < 35 years of age in PTB group. In FTB group there were 195 (26.6%) cases who were ≥ 35 years old and 539 (73.4%) cases who were < 35 years of age, p-value < 0.001. There were 2.12 times higher chances of PTB or females aged ≥ 35 years OR = 2.12 (1.63, 2.76). In PTB and FTB group there were 23 (6.3%) and 22(3%) fathers who were ≤ 18 years and 341 (93.7%) and 712 (97.0%) fathers were > 18 years of age, there was significant association of PTB with lower father's age with OR = 2.18 (1.20, 3.97). In PTB and FTB group there were 218 (59.9%) and 299 (40.7%) father who were ≥ 35 years old and 146 (40.1%) and 435 (59.3%) fathers were < 35 years old, there was significant association of PTB with advanced father's age with OR = 2.17 (1.68, 2.81). In PTB group there were 15 (4.1%) and 14 (1.9%) parents with age of ≤ 18 years and > 18 years and in FTB there were 349 (95.9%) and 720 (98.1%) parents who were ≤ 18 years and > 18 years with significant association between parent's combined age and preterm birth with OR = 2.21 (1.06, 4.63). In preterm and full term birth there were 152 (41.8%) and 259 (35.3%) females who got their in teen ages (OR = 1.31 (1.02, 1.70)) and 49 (13.5%) fathers in PTB and 65 (8.9%) fathers got married in their teen age (OR = 1.60 (1.08, 2.38)) while there were 42 (11.5%) parents in PTB and 40 (5.4%) parents in FTB who got married in their teen age (2.26 (1.44, 3.56)). Using forward conditional logistic regression the final model consisted mother's age ≥ 35 , mother's age ≤18, father's age ≥ 35, parent's marriage <20 years as a predictors of PTB with their respective risk as, OR = 2.949 [1.491, 5.834], OR = 2.168 [1.022, 4.598], OR = 2.446 [1.701, 3.516], OR = 2.906 [1.709, 4.941] while Parent's age < 35 was protective for PTB as well with OR = 0.447 [0.206, 0.968].

TABLE - 1: COMPARISON OF DEMOGRAPHIC CHARACTERISTICS OF MOTHERS, FATHERS AND BOTH PARENTS IN PTB AND FTB GROUPS

Age (years)		Study groups (n= 1098)		*p-value*	Unadjusted OR (95% CI)
		PTB (n=364)	FTB (n=734)		
Age Mother	≤*18*	20 (5.5%)	18 (2.5%)	0.029*	2.13 (1.208, 4.428)
	≥ *18*	344 (94.5%)	716 (97.5%)		
Age Mother	≥*35*	158 (43.4%)	195 (26.6%)	<0.001**	2.12 (1.63, 2.76)
	<*35*	206 (56.6%)	539 (73.4%)		
Age Father	≤*18*	23 (6.3%)	22 (3.0%)	0.009*	2.18 (1.20, 3.97)
	>*18*	341 (93.7%)	712 (97.0%)		
Age Father	≥*35*	218 (59.9%)	299 (40.7%)	<0.001**	2.17 (1.68, 2.81)
	<*35*	146 (40.1%)	435 (59.3%)		
Age parents	≤*18*	15 (4.1%)	14 (1.9%)	0.031*	2.21 (1.06, 4.63)
	≥ *18*	349 (95.9%)	720 (98.1%)		
Age parents	≥*35*	142 (39.0%)	173 (23.6%)	<0.001**	2.07 (1.58, 2.72)
	<*35*	222 (61.0%)	561 (76.4%)		
Mother's age at Marriage	<*20*	152 (41.8%)	259 (35.3%)	0.037*	1.31 (1.02, 1.70)
	≥*20*	212 (58.2%)	475 (64.7%)		
Father's at Marriage	<*20*	49 (13.5%)	65 (8.9%)	0.019*	1.60 (1.08, 2.38)
	≥*20*	315 (86.5%)	669 (91.1%)		
Parent's at Marriage	<*20*	42 (11.5%)	40 (5.4%)	<0.001**	2.26 (1.44, 3.56)
	≥*20*	322 (88.5%)	694 (94.6%)		

** Highly significant (significant at 0.001) & * significant at 0.05

TABLE 2: LOGISTIC REGRESSION MODEL FOR PARENTAL DEMOGRAPHIC RISK FACTORS FOR PRETERM BIRTH

	β	S.E	Wald	d.f	p-value	Adj OR [C.I, 95%]
Mother's age ≥ 35	1.082	0.348	9.655	1	0.002*	2.949 [1.491, 5.834]
Mother's age ≤18	0.774	0.384	4.071	1	0.044*	2.168 [1.022, 4.598]
Father's age ≥ 35	0.894	0.185	23.329	1	<0.001**	2.446 [1.701, 3.516]
Parent's age < 35	-0.806	0.395	4.173	1	0.041*	0.447 [0.206, 0.968]
Parent's marriage <20 years	1.067	0.271	15.525	1	<0.001**	2.906 [1.709, 4.941]
Constant	-1.400	0.115	148.476	1	<0.001**	0.247

** Highly significant (significant at 0.001) & * significant at 0.05

DISCUSSION:

In literature there is a well-known interaction between maternal age and risk of adverse perinatal outcomes, including PTB [19]. Both lower and advanced mother's age are associated with risk of PTB. Teenage mothers carry an increased risk of adverse pregnancy outcomes including an increased risk of delivering earlier than mothers between 20 to 39 years old [9]. Lower maternal age group can also have poor impact on PTB i.e. the risk for PTBs is significantly increased by 24% to 38% and 60% for mother's ≤20, 36-40 and 41-45, respectively, relative to the 20 to 25 year old category [18]. In a Brazilian study where the prevalence of teenage pregnancy was high (29%), the risks of PTB were also increased compared for women aged less than 18 years, 18-19 years and a reference group 25-29 years old (da Silva et al., 2003). Another recent study reported that females with Age <20 is significantly associated with OR = 1.31 [20]. In current study the risk of PTB was 2.31 (OR) times more in females aged ≤ 18 years at time of delivery. The reason behind the risk of PTB among lower age group is may be due to immaturity of the uterine or cervical blood supply that predispose

them to subclinical infection, an increase in prostaglandin production, and a consequent increase in the incidence of preterm delivery. [10]. Advanced maternal age, defined as age 35 years and older at estimated date of delivery, has become increasingly common [21]. In current study the median age of mothers with PTB was higher when compared with mothers delivered FTB, *p-value* <0.001. The females delivered PTB had median age >30 while females delivered full-term birth had median age below 30 years. Another study conducted in 2016 reported that the older maternal age ≥35 years had high risk of PTB with OR = 1.41 [22]. Alike the results of current study another study reported high risk of PTB for elder mother with significant OR as 2.4 with 95% CI (1.3, 4.5) [12]. In this study it was found that there was 2.12 times risk of PTB for females aged ≥ 35. The conception of baby during higher age may be due to family planning, effective birth control, delayed marriage, increasing rates of divorce followed by remarriage, and women's pursuit of higher education and career advancement that all contributes to this trend [23].

Father's age is also associated with risk of PTB as well, a retrospective cohort study reported an increased risk of PTB i.e. OR = 1.15 for teenage fathers [16]. Another study reported that 23% the women were ≥35 years old and among them 3.5% of the women were ≥40 years of age. Only a small percentage (0.6%) of women were <20 years of age [22] while in current study percentage of mother <20 years was higher. Another study also owned the previous findings and reported increased risk of PTB with advanced father's age [17]. However, a study reported no role of advanced father's age and PTB with OR = 1.3 [24] which is clearly a contradiction to previous findings and findings of this study as well. In this study the role of teenage and advanced age of father is established as risk of PTB with risk of 2.18 for teen age and 2.17 for age ≥ 35 years of age. This link can be defended as male reproductive functions alter only slowly over a period of years, although female fertility reaches a natural limit by the occurrence of menopause. The androgen production, spermatogenesis and sexual function are basically sustained lifelong, albeit with age dependent alterations. Increasing evidence shows that advanced paternal age is associated with changes in reproductive functions on different levels. Moreover, the production of reproductive hormones, sexual function, semen production, fertility, pregnancy outcome and the incidence of some birth defects and diseases in offspring are all linked to paternal age [25]. Hence advanced paternal age is associated with

autosomal-dominant disorders and gene mutations, and several findings indicate that genetic factors also play a major role for the timing of the delivery [26].

The average age at marriage for both mother and father in this study was same in both PTB and FTB groups. There is no study that compared age at marriage as a risk of PTB. Moreover, in this study the maternal and paternal ages had combined "U-shaped" effect on PTB. Further this idea was extended by studying marriages in teen age of mother, father separately and for both parents. The OR for mother, father and both parents' marriage in teen age was 1.31, 1.60 and 2.26, respectively. There was significant association of PTB with low maternal and paternal ages (≤18 years) as well as advanced maternal and paternal ages (≥ 35 years), *p-value* <0.001. OR for each low and advanced age of either parent was >1 and was also significant, showing higher risk of PTB for low and advanced maternal and paternal age. Moreover, when low and advanced age of both parents was used as a risk factors together significant association was found with higher risk of PTB for each age categories, OR>1 (*p-value* <0.05). Moreover according to adjusted odds ratio in final model of current study the higher contributor of PTB among demographical variables were, mother's age ≥ 35 , mother's age ≤18, father's age ≥ 35, parent's marriage <20 years as a predictors of PTB.

CONCLUSION:
Through the findings of current study it is concluded that mother's, father's and combined (parent's) lower and advanced age is a major contributor of preterm birth in Pakistan. Even though unadjusted analysis their marriage in teen can also leads to preterm birth. Though in this article only demographic analysis is done and many other related factors were not included. So, further studies are needed to explore further factors as well.

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