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Factors Influencing in Parental Decisions for Fetal Outcome in β-Thalassaemia Major

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ABSTRACT

Objective: To identify the factors that play a role in influencing decisions regarding the outcome of fetuses with ß-Thalassemia major (BTM).

Study Design: Prospective Observational Study.

Place and Duration of Study: Department of Haematology, AFIP, Rawalpindi, Pakistan, from Mar 23 to Feb 24.

Methodology: The Chorionic villus sample was received in laboratory for analysis of ß-Thalassemia mutations. Fetal DNA was extracted, and molecular analysis was performed by Polyacrylamide gel electrophoresis. All families diagnosed with a BTM fetus were followed up, and various factors affecting the decision were identified via a structured questionnaire. Results were entered and analyzed on SPSS version 23.

Results: Over a period of 1 year, a total of 182 samples were received for detection of ß-Thalassemia mutations. There were 48(26.4%) fetuses diagnosed as BTM, 51(28.0%) as normal and 83(45.6%) as ß-Thalassemia Minor. Parents of positive cases were followed up and out of 48 parents who had BTM fetuses, pregnancy was terminated in 43 cases (89.6%) and 5(10.4%) did not opt for termination. The main reason for not terminating the pregnancy were religious beliefs (60.0%), social pressure (20.0%) and twin pregnancy (20.0%). Regarding future use of PND in pregnancies, majority (60.4%) showed willingness, 8.3% were unwilling and 31.3% had no plan to conceive again.

Conclusions: This research has provided valuable insights into the nuanced and intricate landscape of families undergoing PND for ß-Thalassaemia major. The study highlights the need for awareness in the public and directs us to approach religious scholars, public figures, and social media influencers for the needful in addition to the traditional awareness approaches.

Keywords: Chorionic Villous Sampling, Prenatal Diagnosis, Polyacrylamide Gel Electrophoresis, Termination of Pregnancy.

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INTRODUCTION

Thalassaemia is one of the most common monogenic disorders worldwide, with ß-Thalassaemia being particularly prevalent in Mediterranean countries, North Africa, the Middle East, and Southeast Asia.[1] In Pakistan, it is the most common inherited disorder with a carrier prevalence rate of 5.0%.[2] Each year, 5000 children are born with homozygous ß-Thalassaemia mutations. If both parents are carriers of the ß-Thalassaemia gene, there are 25% chances of having a ß-Thalassaemia major fetus.[3]

ß-Thalassaemia major causes severe anemia requiring lifelong blood transfusions and iron chelation therapy.[3] Fortunately, prenatal diagnosis is available in Pakistan for this disease, which permits the carrier parents to know about the mutation status of their fetus well before time. Prenatal diagnosis (PND) of ß-Thalassaemia major is done via chorionic villus sampling, amniocentesis, or free fetal DNA in maternal circulation, thus making it possible for families to make decisions regarding continuing affected pregnancies.[4] This termination decision has a great psychosocial effect on the parents.

The availability of prenatal diagnosis has led to a sharp decline in live births of infants with transfusion-dependent ß-thalassaemia major in many countries over the last few decades.[5] However, the experience of undergoing PND testing and decision-making for an affected pregnancy can be highly distressing and difficult for families.[6] Many factors play a role in decision-making after prenatal diagnosis of ß-Thalassaemia major. There has been limited research on the factors affecting the decision of families undergoing prenatal diagnosis of ß-thalassaemia major.[7] Prenatal diagnosis by chorionic villus sampling is a viable option for prevention of thalassaemia in Pakistan.[8] As chorionic villus sampling can be done at 11-14 weeks in 1st trimester and is considered a relatively safe procedure with least chance of spontaneous abortion post procedure.9 ß-Thalassaemia prevention is possible by effective

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measures such as adaptation of nationwide programs, which has been proven by countries like Italy, Cyprus, and Greece.[10]

The purpose of this study is to contribute towards the prevention of ß-Thalassaemia major within our society by identifying the factors that impede effective measures. This study aims to bridge the gap between the diagnosis and decision making by follow up of families after the result of prenatal diagnosis is finalized. By understanding various barriers, the study aims to play a role in reducing the overall burden of thalassaemia. Healthcare providers will be able to do better counseling of families regarding prenatal diagnosis and decision making. The findings will also help in the genetic counselling of parents of already diagnosed ß-Thalassaemia major children.

METHODOLGY

This was a prospective study that was conducted in the Department of Haematology at the Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan. The study was conducted from Mar 2023 to Feb 2024. Ethical clearance was obtained from Institutional Review Board (IRB) vide reference number FC-HEM22-17/READ-IRB/23/2188. After a full literature search, a sample size of 48 was calculated by using a WHO calculator, keeping 5% margin of error, 95% confidence interval, and 5% prevalence of ß-Thalassaemia trait.[2] A non-probability consecutive sampling technique was employed for selecting the parents. The parents were notified about the study, and informed consent was also taken.

Inclusion Criteria: Families with prenatal diagnosis of ß-Thalassaemia major fetus were included.

Exclusion Criteria: Families diagnosed with ß-Thalassaemia minor or normal fetus and parents who were lost to follow up were excluded.

The Chorionic villus sample was received in laboratory for analysis of ß-Thalassaemia mutations. It was carefully examined with naked eye and under stereomicroscope to ensure sufficient quantity of chorionic villi of fetus. Fetal DNA was extracted from chorionic villi using Chelex method, amplified by ARMS (Amplification Refractory Mutation System) using primers designed for common beta globin gene variants in Pakistani thalassaemia population and resolution of the amplified products was performed by polyacrylamide gel electrophoresis. All the families having fetus with homozygous ß-Thalassaemia mutations were followed up. A structured validated questionnaire in Urdu was employed to know about the educational status of mothers, geographical distribution, previous history of ß-Thalassaemia major children, previous CVS procedures and intention of chorionic villus sampling in future pregnancies. It also included questions to know about their decision regarding termination of pregnancy and various reasons for opting and not opting abortion. Methodology is illustrated in Figure-I.

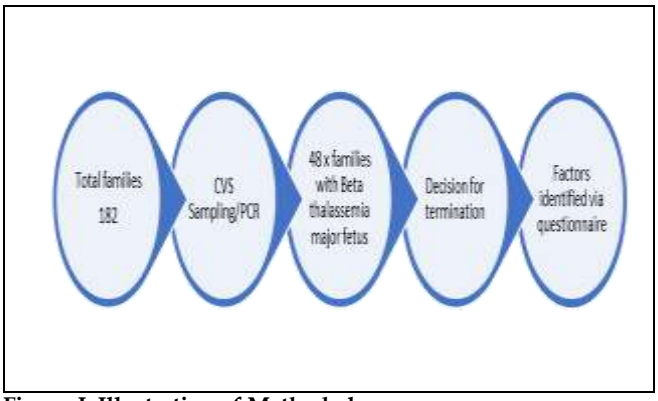

Figure-I: Illustration of Methodo logy

Data was tabulated in Microsoft excel and later analyzed using Statistical Package for Social Sciences (SPSS) version 23.0. For quantitative variables like age of mothers, calculations of the Mean±SD were performed. Qualitative variables like consanguinity, geographical distribution, educational status of mothers and numbers of families that terminated the pregnancy were presented as frequencies and percentages. A Chi-square test was employed for association of various variables and a value of ≤0.05 was used to determine statistical significance.

RESULTS

For research purpose, 182 chorionic villus samples of various families were received in the laboratory spanning over a year. Out of which, 48 (26.3%) families were diagnosed with ß-Thalassaemia major fetus, 83(45.5%) with ß-Thalassaemia minor and 51(28.2%) with the normal fetus. Only 48 families diagnosed with ß-Thalassaemia major fetuses were included in the study, because the decision regarding termination of pregnancy was valid only in these cases. At the time of chorionic villus sampling, the mean age of mothers was 28.9±4.8 years. Educational status of mothers revealed that 8(16.7%) were uneducated, 17(35.4%) had primary education and 23(47.9%) were educated including cumulative groups

of middle, matriculation and intermediate education. Out of 48 families, 40 families (83.3%) had a history of consanguineous marriage, and 8(16.7%) had non-consanguineous marriage. The Geographical distribution of families is given in Table-I.

Table-I: Geographical Distribution in Studied Families (n=48)

Geographical Distribution	
KPK	23(47.9%)
Punjab	17(35.4%)
Sindh	2(4.2%)
Balochistan	2(4.2%)
AK	4(8.3%)

Out of 48 families, 47(97.8%) had a history of a previously diagnosed child with β-Thalassemia major, and 1(2.2%) family had a history of a β-Thalassemia major child in the paternal family. This family received a prenatal diagnosis in the first pregnancy. The 47(97.8%) families had no prior knowledge of the availability of prenatal diagnosis for β-Thalassemia until they had a diagnosed homozygous β-Thalassemia child. The main source of knowledge regarding prenatal diagnosis was healthcare providers. Among these 47 families, 21(44.6%) had a history of a previous chorionic villus sampling procedure, and 26(55.4%) received a prenatal diagnosis for the first time. When asked about prenatal diagnosis in future pregnancies, 29(60.4%) families agreed, 4(8.3%) disagreed (the main reason being that they did not opt for termination of pregnancy, so there was no point in getting CVS done in future), and 15(31.3%) had opted for family planning because they had no plan to conceive in future.

Of 48 families diagnosed with homozygous β-Thalassemia fetuses, 43(89.6%) opted for termination of pregnancy, and 5(10.4%) did not terminate. Among these 5 families, 3 did not terminate mainly for religious reasons. One family had a prior history of termination after prenatal diagnosis, but this time they did not opt for termination due to family pressure. One family had a twin pregnancy. The family with a twin pregnancy did not terminate because one fetus was diagnosed with a homozygous β-Thalassemia mutation and the other with a heterozygous β-Thalassemia mutation. Given the risk of loss of the β-Thalassemia minor fetus, they did not opt for termination despite the option of selective termination of one fetus. The reasons for not opting for termination of pregnancy are illustrated in Table-II.

Table-II: Reasons for Not-Opting Termination of Pregnancy (n=5)

Reasons	
Religious reasons	3(60%)
Family pressure	1(20%)
Twin pregnancy	1(20%)

To compare variables, a Chi-square test was used to assess the statistical significance of the final decision and various factors, including demographic data, that might have influenced the decision-making process. Table-III shows the demographic distribution of families who opted for and against termination of pregnancy. Among the 5 families who opted against termination of pregnancy, 2(40%) were from Khyber Pakhtunkhwa (KPK) and Punjab each, and 1(20%) was from Balochistan.

Table-III: Comparison of Outcome Decision with Various Parameters

Parameters		Termination of Pregnancy		*p*-value
		Yes (n=43)	No(n=5)	
Geographical Distribution	KPK	21(48.8%)	2(40.0%)	0.88
	Punjab	15(34.9%)	2(40.0%)	
	Sindh	2(4.7%)	0(0.0%)	
	Balochistan	1(2.3%)	1(20.0%)	
	AK	4(9.3%)	0(0.0%)	
Consanguinity	Yes	36(88.4%)	4(40.0%)	0.83
	No	7(11.6%)	1(60.0%)	
Education of Mother	Educated	39(90.7%)	1(20.0%)	<0.001
	Uneducated	4(9.3%)	4(80.0%)	
Previous CVS	Yes	24(55.8%)	0(0.0%)	0.01
	No	19(44.2%)	5(100.0%)	
CVS in future pregnancy	Yes	26(60.4%)	3(60.0%)	0.5
	No	3(7.0%)	1(20.0%)	
	Family Planning	14(32.6%)	1(20.0%)	

**KPK- Khyber-Pakhtunkhwa*
AK – Azad Kashmir
CVS- Chorionic Villus Sampling

Out of 43 families who opted for termination of pregnancy, 39(90.7%) mothers were educated, and 4(9.3%) mothers were uneducated. Out of families who did not opt for termination, 1(20%) mother was educated, and 4(80%) were uneducated. All the 5(100%) families who did not opt for termination of pregnancy had no previous history of a chorionic villus sampling procedure for prenatal diagnosis.

DISCUSSION

Our study was conducted in a northern region of Pakistan, and the majority of families belonged to Punjab and KPK. Consanguinity was higher (83.3%) in our study, as β-thalassemia is an inherited disorder, and its incidence is higher with consanguineous marriages. Beta-thalassaemia major is an inherited blood disorder, and prenatal diagnosis plays a crucial role in the management and prevention of this debilitating condition, particularly in regions with a high prevalence, like Pakistan.[11]

This finding is similar to those of previous studies by Zaidi *et al*., which reported consanguinity rates of 88% and 81.7%, respectively.[12] The incidence of ß-Thalassaemia major fetus after prenatal diagnosis in our study was 26.4%, which is in comparison to the study of Javed *et al*., in which the incidence of ß-Thalassaemia major was 37% after prenatal diagnosis. This shows the decline in the incidence of beta thalassaemia due to availability of prenatal diagnosis. In the same study, intention to get the CVS done in future pregnancies was 67%, which is similar to our study, as 65.3 % families had the intention to get the CVS done in subsequent pregnancies.[13]

The religious limitations warrant an early diagnosis, as reported by Ebrahim *et al*., which is possible through chorionic villus sampling. However, there is a need for intervention to raise awareness of religious recommendations.[14] Our study highlighted the religious aspect, as 3(60%) of 5 families cited religious reasons for not terminating the affected pregnancy. Moreover, in the 4th family that did not opt for termination of pregnancy due to family pressure, the main reason was religious. This finding contrasts with a study by Ansari *et al*., in which religion was not an impediment to obtaining prenatal diagnosis or to the families' decisions to terminate pregnancy.[15] However, this study showed that religious values affect the decision-making process regarding termination of pregnancy after prenatal diagnosis. This is also contrary to the fact reported by Bozdar *et al*., that families obtain prenatal diagnosis, but once the decision is made, various reasons come into play.[16]

A six-year-experienced Ehsan *et al*., presented a case series of twin pregnancies, in which selective termination of the affected fetus was studied. Chorionic villus sampling and selective termination of affected fetus were found to be safe procedures.[17] The 5th family in this study, who did not opt for termination, were having twin pregnancy with one homozygous fetus and other as heterozygous for ß-Thalassaemia mutations. The family was given the option of selective fetal termination, but opted against it due to the risk of loss of the heterozygous fetus. A significant correlation (p-value<0.001) was found with the education of mothers, as in 4(80%) out of 5 families who did not opt for termination of pregnancy, the mothers were uneducated. The previous history of CVS procedure also showed a significant correlation (p-value 0.01) with the termination of pregnancy, as the 100% of families who did not opt for termination of pregnancy got prenatal diagnosis done for the 1st time. These findings is relatable with study conducted by Manzoor *et al*.,

Monni *et al*., studied a group of families in a high-risk population of Sardinia, where the carrier rate of the β-thalassemia gene was 10-12%. They employed various techniques to prevent β-thalassemia major, including molecular screening of couples, prenatal diagnosis by chorionic villus sampling (CVS), and preimplantation genetic diagnosis (PGD). This study concluded that, due to these effective measures at their prenatal center, the incidence of β-thalassemia children was reduced to 3-5 per year.[19]

It is noteworthy that the study was conducted in a region with limited resources and socio-cultural barriers, which can hinder access to prenatal diagnosis and termination services. Cultural beliefs, religious values, and societal stigma surrounding prenatal diagnosis and termination of pregnancy can pose significant challenges.[20,21] Addressing these barriers through culturally sensitive approaches, involving religious leaders, and promoting open discussions within communities is crucial for the successful implementation of thalassaemia prevention programs in Pakistan.[22]

LIMITATIONS OF STUDY

The majority of the study population was from Northern Pakistan, as the study was conducted in Rawalpindi. A larger sample size could have led to better conclusions. Moreover, socioeconomic variable was not studied and should be part of future studies.

CONCLUSION

ß-Thalassaemia Major is a debilitating yet preventable disease. Effective measures for its prevention include public awareness and screening before marriage. Parents and Society shall be made aware of the prenatal diagnosis of ß-Thalassaemia by chorionic villous sampling and regarding termination of pregnancy. In struggling economy like Pakistan where poverty rate is high and availability of bone marrow transplant is limited, it is not possible to cope up

with the rising trends of this disease. Therefore, prevention strategies are the need of the hour, and the impediments and factors identified in this study point to the areas that also need immediate attention. The study also highlights the need for awareness in the public and directs us to approach religious scholars, public figures and social media influencers for the needful in addition to the traditional awareness approaches.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MA & MB: Data acquisition, data analysis, critical review, approval of the final version to be published.

HSM & RM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AK & AK & SSS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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