International Journal of Contemporary Pediatrics
John ST et al. Int J Contemp Pediatr. 2022 Jun;9(6):566-570
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20221375

Original Research Article

Screening of mothers to detect Down syndrome: a practical approach in a resource limited setting

Shaji Thomas John*, Kizhanipurath Gayathri

Department of Paediatrics, Baby Memorial Hospital, Kozhikode, Kerala, India

Received: 03 April 2022
Revised: 28 April 2022
Accepted: 04 May 2022

***Correspondence:**
Dr. Shaji Thomas John,
E-mail: doctorshaji@hotmail.com

ABSTRACT

Background: Advanced maternal age, history of abortion and/or bleeding in pregnancy are risk factors for the birth of a chromosomally abnormal child. This study was done to find out their relationship especially in Down syndrome (DS).
Methods: Retrospective observational study was done in children with DS and their mothers, from a major referral institution in India over a period of 20 years. The prevalence of abortion/bleeding in pregnancy with the age of mothers were analysed using statistical package for social sciences (SPSS) V20 software and compared in all the cytogenetic profiles.
Results: In mothers less than 35 years 21.8% had abortion, 8% had bleeding and 4.5% had both abortion and bleeding. In mothers more than 35 years 25% had abortion, 7.3% had bleeding and 4% had both abortion and bleeding. Thus 34.5% had abortion/bleeding in mothers less than 35 years and 36.8% in those above 35 years. 15.25% mothers were more than 35 years. When the individual cytogenetic pattern and the prevalence of abortion/bleeding were analysed in maternal age group less than 35 years; a higher prevalence was seen in the non-disjunction group (34.2%), followed by translocation (24%) and mosaic (21.42%). In maternal age group >35 years prevalence was high, though not statistically significant, in the mosaic group (66.67%) followed by non-disjunction (43%).
Conclusions: Mothers with a history of abortion/bleeding and those above 35 years constituted 44.7%. Ideally all pregnant women should be screened for chromosomal aneuploidies, but in resource limited countries screening should be done at least in the above noted high risk groups.

Keywords: Abortion, Bleeding, Maternal age, Down syndrome

INTRODUCTION

Chromosomal abnormalities especially DS is one of the most common causes of intellectual disability. The incidence of DS in live births is approximately 1 in 733, whereas the incidence at conception is more than twice that rate, which is accounted by early abortions.[1] It is estimated that in about 15 to 20% of clinically recognizable pregnancies, chromosomal abnormalities form the most common cause of spontaneous pregnancy loss in the first trimester.[2,3] In most cases, it is too early to determine the exact cause of the abnormality. With increasing gestational age, risk of pregnancy loss decreases and is relatively low after 15 weeks of gestation in a genetically normal fetus.[4]

The incidence of fetal chromosomal abnormalities increases with increasing maternal age, thus maternal age is an important predictor in the risk of miscarriage. The risk of miscarriage in women aged 20 to 30 years with less than 20 weeks gestation is 8.9% and it increases to 74.7% for women over 40 years.[5] Prior obstetrical history

of miscarriage is another important predictor in the risk of early pregnancy loss. The risk of miscarriage is 20% after 1 miscarriage, 28% after 2 consecutive miscarriages, and 43% after 3 or more miscarriages.[6]

Cytogenetic analysis of chorionic villi can be done to know the cause of fetal loss and to assess the risk of recurrence.[7] Knowledge about the status of the fetus will be helpful to the parents and their families to take an appropriate decision. In countries where termination is permitted (usually before 20 weeks only), a diagnosis prior to that is absolutely essential. Mothers who wish to continue with the pregnancy can be primed to accept the child and initiate early interventional therapies.

Antenatal diagnosis is sparingly utilized, probably due to resource constrain and lack of awareness amongst health personnel. Only high-risk women were offered testing in the past as only invasive tests were available. Non-invasive screening tests are available now and it should be offered to all pregnant women irrespective of age. Antenatal tests available are of two types: screening tests and diagnostic tests. Initially non-invasive screening should be offered to determine the probability of having a baby with chromosomal abnormalities, as it carries no risk to the mother or fetus. If the screening tests show a high probability, diagnostic tests should be offered, but they are invasive and carry a risk of miscarriage (0.5%-1%). The probability of having a baby with chromosomal abnormality, especially DS, is arrived at by combining maternal details and the results of the ultrasound findings and serum markers.[8]

Antenatal diagnostic screening tests for aneuploidy especially DS are as noted below:

Dual marker test (DMT)

This is a first trimester screening test and usually done between 10 and 14 weeks of gestation.[9] Pregnancy associated plasma protein A (PAPP-A) and free beta human chorionic gonadotrophin (ßhCG) are the markers done in this test.[10]

Triple marker test (TMT)

This second trimester screening test is done between 15 and 20 weeks of pregnancy.[11,12] Alpha fetoprotein (AFP), total ßhCG and unconjugated estriol (UE3) are the markers used.[13]

Quadruple marker test (QMT)

This is also a second trimester screening test done between 15 and 20 weeks of gestation.[12] AFP, total ßhCG, UE3 and inhibin A are the markers used. All the above three tests calculate the risk for Trisomy 18, Trisomy 21 and open neural tube defects.

Ultrasound markers for aneuploidies

An ultrasound marker is an anatomical finding which is not an abnormality, it may be present in normal fetuses too, but when present indicates an increased risk for fetal aneuploidy. Several first and second trimester markers are available.

Testing of cell free DNA

Cell free fetal DNA (deoxyribo nucleic acid) in maternal blood represents extracellular DNA which originates from trophoblastic cells.[14] The cell free fetal DNA represents only 3% of the total cell free circulating DNA in early pregnancy, rising to 6% in late pregnancy; while the majority of cell free DNA in maternal blood originates from the mother.[15] After delivery the cell free DNA is rapidly cleared from the maternal circulation making it specific to that pregnancy. If a fetus has Down syndrome, there will be an increase in the quantity of chromosome 21 in the maternal blood. The sequencers are sensitive enough to detect even very small amount of chromosome 21 with relatively little cell free fetal DNA.[16] The cell free fetal DNA screening test, which is non-invasive, can be done at any time after 10 weeks and it has 99.2% specificity and 100% sensitivity.[17]

The present study was done to know the correlation between maternal age, history of abortion, bleeding in current pregnancy and its association with Trisomy 21, which is the classical example of chromosomal aneuploidy. It was also enquired whether antenatal diagnosis was offered to the mothers during the pregnancy.

METHODS

A retrospective observational study was done of children with DS and their mothers who attended the DS clinic at Baby Memorial Hospital, Calicut, Kerala state, India. All cases between November 2000, when the DS clinic was started and July 2020 were taken and de-identified by an external party. The case records that had a proper data recorded were included. The data considered were a proper history, which included maternal age at the time of birth of child with DS, order of birth, history of spotting or bleeding in current pregnancy, past history of abortion and whether ante-natal diagnosis was offered. Incomplete case records were excluded and the first 800 case records that were eligible to be included were taken up for the study.

The variables were entered in an excel sheet and the prevalence of abortion/bleeding in pregnancy in mothers of children with DS were studied and compared in all the cytogenetic profiles. The data was analysed using statistical package for social sciences (SPSS) V20 software. Statistical tests were 2-sided and statistical significance was set at level 0.05. Details are given in the flow chart (Figure 1).

Ethical approval was granted by the institutional ethics committee, Baby Memorial Hospital vide approval. The institutional ethics committee is accredited by National accreditation board for hospitals and healthcare providers and registered with the drug controller general of India as per order.

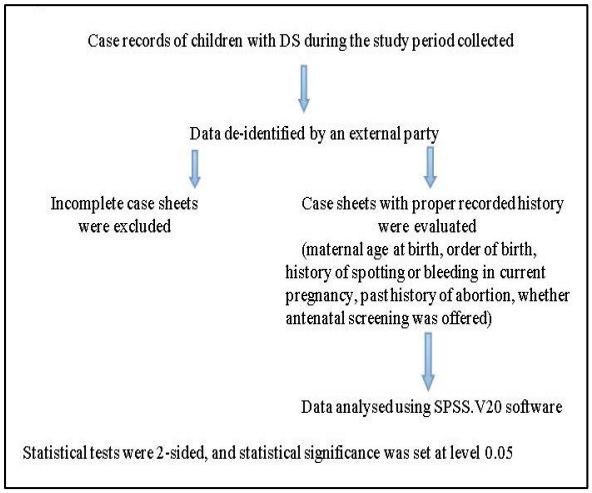

Figure 1: Flow chart.

RESULTS

Data from 800 cases were included in the study. Maternal age at birth of the children ranged from 16 to 50 years and the mean maternal age at the time of delivery was 28 years (SD 6.45).

Majority of the mothers were in the age group 20-30 years. 655 (81.87%) of children were born to mothers younger than 35 years, which included 96 (12%) under 20 years. Only 122 (15.25%) were born to those older than 35 years. In 23 (2.88%) mothers, the age at birth of child was not recorded. The age wise split up of mothers is shown in Figure 2. The birth order of children with Down syndrome ranged from 1 to 10. Overall, more than half of them were of first and second order births.

The maternal age and history of abortion/bleeding were analysed. It was found that in mothers aged <35 years the prevalence of abortion, bleeding and both abortion and bleeding were 143 (21.8%), 53 (8.09%) and 30 (4.58%) respectively, with an overall prevalence of 34.5%. In mothers aged >35 years it was found to be 31 (25.4%), 9 (7.3%), and 5 (4%) respectively, the overall prevalence being 36.8% (Table 1). However, the p value (0.343) was not significant.

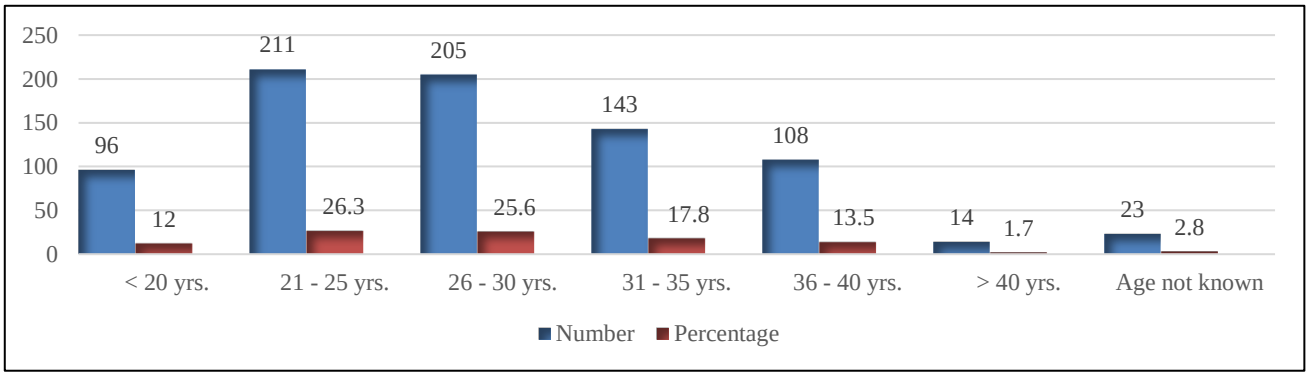

Figure 2: Maternal age at the time of birth of the child.

Table 1: Abortion and bleeding among the age groups below and above 35 years.

Abortion/bleeding	Age <35 years (n=655)	Age >35 years (n=122)	All ages (n=777)	Unknown* (n=23)
Abortion alone	143	31	174	0
Bleeding alone	53	9	62	1
Both abortion and bleeding	30	5	35	1
Total	226	45	271	2
%	34.5	36.8	34.8	-

Fisher's exact test p=0.343. *Age not specified in the case records.

In less than 20 years 13.5% of mothers had abortion/bleeding/both abortion and bleeding. As age advanced it was showing a progressive increase in the prevalence; between 36 and 40 years it was 53.7% which is more than four times (Table 2).

Prevalence of abortion/bleeding in various cytogenetic profiles were also studied. Of the total 582 cases where cytogenetic studies were done, non-disjunction constituted 87.5%, translocation 9.45% and mosaics 3.09%. In mothers <35 years, in the non-disjunction

group, the prevalence of abortion, bleeding and both abortion and bleeding were 83 (20.2%), 36 (8.8%) and 21 (5.1%) respectively. In mothers >35 years it was 26 (30%), 8 (9.3%) and 3 (3.4%) respectively.

In the translocation group in mothers aged <35 years the prevalence was 7 (12.9%), 3 (5.5%) and 3 (5.5%) respectively. No case of abortion or bleeding was seen in mothers aged >35 years in this group.

Table 2: Abortion and bleeding in the various age slabs.

Age	Total mothers (n=777)	%	Abortion/ bleeding/ both (n=295)	%
< 20	96	12.35	13	13.5
20-25	211	27.15	65	30.8
26-30	205	26.38	84	40.9
31-35	143	18.40	68	47.5
36-40	108	13.89	58	53.7
41-45	12	1.54	7	58.3
46-50	2	0.25	2	100

p<0.0001

Table 3: Abortion and bleeding among the various cytogenetic profiles.

	Non disjunction			Translocation			Mosaic		
	<35 yrs n=409	>35 yrs n=86	Unknown n=14	<35 Yrs n=54	>35 yrs n=0	Unknown n=1	<35 yrs n=14	>35 yrs n=3	Unknown n=1
Abortion alone	83	26	0	7	0	0	2	1	0
Bleeding alone	36	8	1	3	0	0	0	0	0
Both abortion and bleeding	21	3	0	3	0	0	1	1	0
Total	140	37	1	13	0	0	3	2	0
Percentage	34.2	43	-	24	0	-	21.42	66.67	-

<35 years: p=0.746. >35 years: p=0.150.

In mothers aged <35 years in the mosaic group, the prevalence of abortion and both abortion and bleeding were 2 (14.2%) and 1 (7.1%). In mothers >35 years it was 1 (33%) each. No case of isolated bleeding was seen in this group (Table 3).

On analysis of the individual cytogenetic groups and the prevalence of abortion/bleeding in maternal age group <35 years, a higher prevalence was seen in the non-disjunction group (34.2%), followed by translocation (24%) and mosaic (21.42%). Whereas in maternal age >35 years a higher prevalence of abortion/bleeding was seen in the mosaic group (66.67%) followed by non-disjunction (43%). These were not statistically significant (p=0.150).

None of the mothers except two were offered antenatal screening according to the history recorded. These two mothers did not want termination and were counselled and primed to accept the baby. Others who might have been offered antenatal screening could probably have terminated the pregnancy.

DISCUSSION

Spontaneous miscarriages are strongly associated with fetal chromosomal abnormalities as well as advanced maternal age. Chromosomal abnormalities are observed in 50-70% of spontaneous miscarriages; with DS being the most common abnormality.[17-19] Cytogenetic analysis of miscarriages has shown a higher prevalence of chromosomal abnormalities in the first trimester when compared to second and third trimester of pregnancy.

Bleeding per vaginam (PV) might be a pre-runner to spontaneous abortion and thus can be a pointer towards a genetically abnormal child. In our study, of the total mothers 34.8% had abortion in the previous pregnancy or bleeding in the current pregnancy or both. The prevalence of bleeding PV/abortion was almost similar in age groups less than 35 and those above 35 years. 34.5% of mothers <35 years and 36.8% >35 years had history of abortion/bleeding. As already known, we also got a higher prevalence of abortion /bleeding as age advanced.

It is well documented that a maternal age of 35 years carries a risk of 1 in 365 for having a child with DS and a risk of 1 in 30 at age 45 years.[20] When mothers aged above 35 years (122) and those with history of abortion and bleeding in less than 35 years (226) were studied, it was found that they constituted 44.7% of all the mothers. So, if screening for the above group of mothers had been done during the ante-natal period, 44.7% of the babies with DS could have been picked up. Ideally with this high rate, all mothers should be screened antenatally.

Several antenatal screening tests are available for DS, but knowledge about the appropriate test and its timing with the need for pre and post test counselling may not be known to the primary medical caregivers. Due to the absence of any definite guideline and the added lacunae in awareness, the optimum benefits of these screening methods do not reach the public.

Limitation of the study

Since this was a retrospective study, it was not possible to have a control group with mothers of normal children.

CONCLUSION

Antenatal screening for aneuploidies should be made mandatory for all pregnant women, but in a resource limited country, antenatal screening should be done at least in all pregnancies above the age of 35 years and in mothers who have an history of abortion or bleeding/spotting PV in the current pregnancy. This will help to identify, and if possible, reduce the birth of children with chromosomal abnormalities.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. K. G. Alexander, chairman and managing director of Baby Memorial Hospital, for all the support given in the running of the DS clinic; Saji S. Mathew chief operating officer, for all the information technology related help rendered in data acquisition.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Lee B. Down syndrome and other abnormalities of chromosome number. In: Kliegman RM, Blum NJ, Tasker RC, eds. Nelson textbook of Pediatrics. 21st ed. Elsevier. 2020;658-64.
2. Hassold TJ, Jacobs PA. Trisomy in man. Annu Rev Genet. 1984;18:69-97.
3. Petracchi F, Colaci DS, Igarzabal L, Gadow E. Cytogenetic analysis of first trimester pregnancy loss. Int J Gynaecol Obstet. 2009;104:243-4.
4. Wyatt PR, Owolabi T, Meier C, Huang T. Age-specific risk of fetal loss observed in a second trimester serum screening population. Am J Obstet Gynecol. 2005;192(1):240-6.
5. Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ. 2000;320(7251):1708-12.
6. Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. BMJ. 1989;299(6698):541-5.
7. Soler A, Morales C, Mademont-Soler I, Margarit E, Borrell A, Borobio V et al. Overview of Chromosome Abnormalities in First Trimester Miscarriages: A Series of 1,011 Consecutive Chorionic Villi Sample Karyotypes. Cytogenet Genome Res. 2017;152(2):81-9.
8. Puri S, Morris J. Antenatal diagnosis: Giving the news. In: Newton RW, Puri S, Marder L, eds. Down syndrome Current perspectives. Mac Keith, 2015:13-22.
9. Alldred SK, Takwoingi Y, Guo B, Pennant M, Deeks JJ, Neilson JP et al. First trimester serum tests for Down's syndrome screening. Cochrane Database Syst Rev. 2015;2015(11):CD011975.
10. Wald NJ, Kennard A, Hackshaw AK. First trimester serum screening for Down's syndrome. Prenat Diagn. 1995;15(13):1227-40.
11. Huderer-Duric K, Skrablin S, Kuvacic I, Sonicki Z, Rubala D, Suchanek E. The triple-marker test in predicting fetal aneuploidy: a compromise between sensitivity and specificity. Eur J Obstet Gynecol Reprod Biol. 2000;88(1):49-55.
12. Alldred SK, Deeks JJ, Guo B, Neilson JP, Alfirevic Z. Second trimester serum tests for Down's Syndrome screening. Cochrane Database Syst Rev. 2012;(6):CD009925.
13. Wald NJ, Kennard A. Prenatal biochemical screening for Down's syndrome and neural tube defects. Curr Opin Obstet Gynecol. 1992;(2):302-7.
14. Alberry M, Maddocks D, Jones M, Abdel Hadi M, Abdel-Fattah S, Avent N et al. Free fetal DNA in maternal plasma in anembryonic pregnancies: confirmation that the origin is the trophoblast. Prenat Diagn. 2007;27(5):415-8.
15. Lo YM, Tein MS, Lau TK, Haines CJ, Leung TN, Poon PM et al. Quantitative analysis of fetal DNA in maternal plasma and serum: implications for noninvasive prenatal diagnosis. Am J Hum Genet. 1998;62(4):768-75.
16. Rafi I, Chitti L. Cell free fetal DNA & non-invasive pre-natal diagnosis. British Journal of General Practice. 2009;59(562):e146-8.
17. Sparks AB, Struble CA, Wang ET, Song K, Oliphant A. Noninvasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for Trisomy 21 and Trisomy 18. Am J Obstet Gynecol. 2012;206(4):319-9.
18. Yuan SM, Liao C, Li DZ, Huang JZ, Hu SY, Ke M et al. Chorionic villus cell culture and karyotype analysis in 1983 cases of spontaneous miscarriage. Zhonghua Fu Chan Ke Za Zhi. 2017;52(7):461-6.
19. Kajii T, Ferrier A, Niikawa N, Takahar H, Ohama K, Avirachan S. Anatomic and chromosomal anomalies in 639 spontaneous abortuses. Hum Genet. 1980;55:87-98.
20. Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. Br J Obstet Gynaecol. 1987;94(5):387-402.

Cite this article as: John ST, Gayathri K. Screening of mothers to detect Down syndrome: a practical approach in a resource limited setting. Int J Contemp Pediatr 2022;9:566-70.