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Research Article

Advanced Maternal Age, also an Important Risk Factor for Down Syndrome in African Black Population. A Nine - Year Experience in Rwanda and Burden Outcome

Janvier Hitayezu[1,2], Védaste Ndahindwa[3], Seraphine Murorunkwere[1], Janvier Ndinkabandi[1], Annette Uwineza[1], and Leon Mutesa[1]*

[1]*Center for Human Genetics, University of Rwanda, Rwanda*
[2]*Department of Pediatrics, University of Rwanda, Rwanda*
[3]*School of Public Health, University of Rwanda, Rwanda*

***Corresponding author**
Leon Mutesa, Center for Human Genetics, University of Rwanda, Kigali & Butare, Rwanda; Tel: 250-0-7 8845-1013; Email: lmutesa@gmail.com

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Keywords

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Abstract

Background: Down syndrome is the most common chromosome abnormality recognized to cause intellectual disability in all human ethnic groups worldwide. Advanced maternal age has been identified as risk factor associated with underlying mechanism of chromosome 21 non-disjunction error leading to free trisomy 21, the most frequent form of Down syndrome. A shift to younger maternal age for Down syndrome births appreciated in some recent studies, earlier data showing majority of Down syndrome infants born to young mothers in Rwanda and regularly diagnosed cases from young mothers have prompted us to conduct a research to verify the magnitude of maternal age effect on Down syndrome births.

Methods: A cross-sectional survey was conducted at the Rwanda Center for Human Genetics. Cases of Down syndrome patients diagnosed from December 2006 till February 2016 were identified with respective maternal age at birth. Using Stata SE 13, the Wilcoxon signed test allowed to compare the maternal age for these patients with the reference median age from the 2010 Rwanda Demographic and Health Survey (RDHS).

Results and Conclusion: Of 320 patients diagnosed over this period, maternal age was recorded only for 286 patients, of them 276 patients had free trisomy 21 and the mean maternal age at which they were born was 34.6 years [95% CI: 33.8-35.5]. The z test statistic calculated at the reference median maternal age gave a p-value < 0.0001.

That is the maternal age at birth of Down syndrome patients was significantly higher than the maternal age for childbirth in the Rwanda general population.

ABBREVIATIONS

CHDs: Congenital Heart Defects; CHUB: Centre Hospitalier Universitaire de Butare; CHUK: Centre Hospitalier Universitaire de Kigali; DS: Down syndrome; NDJ: Non Disjunction; RDHS: Rwanda Demographic and Health Survey

INTRODUCTION

Down syndrome (DS), the most common chromosome abnormality among live born infants and the most frequent recognizable genetic cause of intellectual disability in all human ethnic groups across the globe, is caused by trisomy 21 due to non-disjunction (NDJ) error during meiosis at parental

gametogenesis for the majority (about 95%) of cases [1]. With an estimated incidence of Down syndrome of 1 in 700 live births, advanced maternal age and altered meiotic recombination have been identified as 2 independent and strong maternal correlates associated with underlying mechanism of chromosome 21 non-disjunction, particularly for the mother owing to developmental differences of oogenesis compared with spermatogenesis making oocytes more vulnerable to malsegregation during their arrested phase of cell division [2,3]. Advanced maternal age (defined as age 35 years or more) alone was initially used to screen pregnancies for Down syndrome [4,5]. Translocation and partial trisomy, other 2 chromosomal abnormalities responsible for Down syndrome, and accounting for about 5% of all Down syndrome cases are not related to maternal age; the paternal age also has no influence on chromosome 21 non disjunction [6].

Since the discovery that Down syndrome is caused by trisomy of chromosome 21, subsequent studies have ensued aiming at identifying the etiologic factors associated with the underlying mechanism of chromosome 21 NDJ. Chromosomal NDJ is considered complex and multi-factorial and its underlying mechanisms are associated with age dependent risk factors while others are age-independent. Other etiologic and risk factor hypotheses for Down syndrome have emerged like biological and/or genetic aging hypotheses, gene polymorphism in folate metabolic pathways, etc.; and reported results have been conflicting or need further evidence [3,7,8].

A shift to younger ages for Down syndrome cases has been appreciated in some recent studies in India, and analyses of 294 cases in a retrospective study on maternal age and Down syndrome found its occurrence to be different in different age groups [9,10]. Researchers recommended further studies on larger samples to more characterize this relationship. Most of epidemiological data reported on Down syndrome are statistical estimates from developed countries [11]. Differences (genetic, racial, environmental, etc.) between black African population and developed world make these data hardly reliable [11], but very few studies and data specific for Africa can be found owing to the lack of genetic tests infrastructure, qualified personnel and poverty.

Since karyotype analyses have started in Rwanda from 2006, we have been observing number of younger mothers giving birth to infants with Down syndrome. This is in part thought to be related with the fact that Rwandan mothers give birth at young age in general on one hand, or on the other hand advanced maternal age has little impact on the occurrence of DS births as it has been widely accepted in the literature. To date, epidemiological data for DS are insufficient at national level since there has been no mechanism of its systematic screening/detection. However, the disorder is one of the most reasons to seek genetic consultation in Rwanda and available data are from cases seen at the center for human genetics with an advantage of being the only institution in the country where the diagnosis can be confirmed. Those data reflect but underestimate the degree of the problem in the general population given a number of patients that may go undetected. Out of 345 patients consulted the department of genetics up to 2010, 65 cases of Down syndrome (18.8%) were confirmed on karyotype analyses [12]. A study done earlier in 2007 had shown young women to represent the majority of mothers with free trisomy 21 births in Rwanda (72 ≤ 34.4%) years were old [12,13]; but this was done on small sample (n=29) before the beginning of genetic tests in the country.

These data, with regularly diagnosed cases of DS infants born to young mothers, have led us to think that DS births in Rwanda are more common in young mothers and may have other related risk factors than advanced maternal age. We conducted a research to examine whether those births occur more frequently as the maternal age increases in Rwanda or if other risk factors are yet to be discovered. Maternal ages for DS cases diagnosed at the Center for Human Genetics in Rwanda over a period of more than 9 years were compared with the maternal ages in the reference population of Rwanda using data from the Demographic and Health Survey.

MATERIALS AND METHODS

Study design, site and period

A cross-sectional survey was conducted at the Rwanda Center for Human Genetics. The center is unique in such a way that it is the only institution in the country that can offer karyotype testing thanks to its medical genetics laboratory located in Butare (School of Medicine/University of Rwanda), southern province. The study, mainly retrospective with some cases traced prospectively from December 2015 when the project was started, covers a period of more than 9 years for data collection since the beginning of genetic testing, mainly karyotype in Rwanda from December 2006 till February 2016. The study per se lasted 5 months from December 2015 till April 2016 with the completion of a final report. The center is still young with currently 2 medical geneticists (PhD holders) doing genetic outpatient clinics in 3 referral hospitals, the 2 University Teaching Hospitals in Kigali [CHUK] and Butare [CHUB] as well as the Rwanda Military Hospital in Kigali. The medical genetics laboratory can currently only perform karyotype locally while DNA is extracted and sent to partner laboratories (mainly at the Center for Human Genetics, University of Liege, Belgium) for molecular analyses when needed. With basic equipment now available, molecular analyses are expected to start in the near future at the center locally.

Patients

Three hundred and twenty patients (out of a total of 1560 tested at the center, or 20.5%) with DS were diagnosed over the period time considered for data collection. The male to female sex ratio was almost 1:1 (or 163 males over 157 females). The mean age at the time of testing was 20.5 months (615.6 days, 95% CI: 505.6- 725.5); 30 babies (9.4%) were tested by age 29 days, 173 (or 63.64%) by their 1st anniversary, and 246 (or 86.52%) by age 3 years, while 3.13%(or 10 patients) were aged above 10 years. The younger age at the time of consultation/test was the birth date for 1 baby, while the oldest was 17 years [Figure 1]. Of the 304 patients with identified origin, 8 of them were foreigners (mainly Congolese from refugee camps in Rwanda) while the remainder, 97.3% were nationals from all the provinces (in 29 out of the 30 districts) of the country.

Genetic tests

Cytogenetic tests were performed on peripheral venous blood

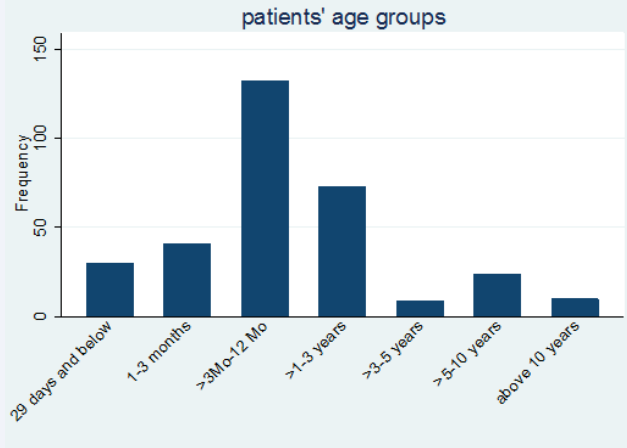

Figure 1 Number of Down syndrome cases in different age groups.

for each patient at the medical genetics laboratory in Butare. Chromosome preparations were made from 72-h peripheral blood lymphocyte cultures according to conventional protocols and routinely stained with Quinacrine. The standard karyotype was performed on Q-banded metaphase spreads and analyzed according to the International System for Human Cytogenetic Nomenclature guidelines. FISH techniques performed in the Belgium were used to detect a rare case of translocation between chromosome 21 and Y sex chromosome.

Reference population

With its more than 10,537,222 people as of 2012, Rwanda ranks among countries with the highest average annual population growth rate in Central and East Africa with 2.6% [14]. The total fertility rate remained relatively stable and fluctuated around 6 from 1992 through 2008 to decline to 4.6 and 4.2 children per woman in 2010 and 2014 respectively; these national demographic data are obtained thanks to two regular mechanisms for surveillance of the Rwandan population dynamics, the general population and Housing Census and the Demographic and Health Survey, DHS [15,16]. For DHS and regarding fertility and childbearing information, all women in their reproductive age between 15 and 49 years from selected households are eligible for the survey; the latest DHS in Rwanda conducted in 2014-2015 had preliminary results almost similar to that of its immediate preceding of 2010 [15,16]. We used data of the 2010 Rwanda DHS and obtained data on childbirth in Rwanda, which think reflect well the situation of our period considered for data collection. Mothers in our study are well part of this population but their number is considered negligible to impact the national trends.

Statistical analyses

With descriptive statistics, Stata SE 13 software was used to determine frequencies of DS cases according to different maternal age/age groups and the mean maternal age at birth for this group of children. Since there was no control group to test whether the maternal age at birth of these DS patients is different from that in the general population, we used data from the 2010 RDHS as mentioned above. During the 2010 RDHS, 13,671 women in the reproductive age from 15 years to 49 years were interviewed. Of them, 8, 094 women had given birth to at least one child with a total of 32,639 children. The mean and median ages at which each woman gave birth were calculated from different ages when her respective children were born and from individual maternal mean and median ages. And we were able to compute the mean and median ages for the whole population of women enrolled in the survey. The mean maternal age was 27.1 years, while the median was 26.3 years. When these parameters were calculated for the last childbirth, the mean maternal age was found to be 28.9 years, while the median was 29.3 years. After testing the normality, data in our sample were found to be not normally distributed and a non-parametric test (the Wilcoxon signed-rank test) applied to compare the maternal age in our study sample to reference medians $\alpha = 0.05$, in the 2010 RDHS. At a significance level the test statistic calculated has allowed statistical decision and conclusion to reject the null hypothesis.

Ethical considerations

The study protocol was submitted to and approved by Institutional Review Board of the University of Rwanda College of Medicine and Health Sciences (UR, CMHS IRB). Approval Notice: No 036/CMHS IRB/2016.

RESULTS AND DISCUSSION

In present study, free trisomy 21 was found in 308 patients (or 96.2%) with one of them having double trisomy (chromosomes 21 and X: 48, XXX, + 21). Translocation cases were found in 11 patients (or 3.4%), 10 of them being robertsonian translocations (6 cases of isochromosome 21, two cases of translocations between chromosomes 21 and 22, one case between chromosomes 15 and 21 and one case between 14 and 21) with a rare translocation between chromosome 21 and the Y sex chromosome. One patient was found to have 2 cell lines with a standard karyotype 47, XY, + 21 and a robertsonian translocation involving chromosomes 13 and 21. There was also one patient with free/standard trisomy 21 associated with inversion of chromosome 9 segments [47, XY, + 21 inv9 (p11; q13)] (Table 1 A,B). More than 50% of patients were diagnosed only over the last 3 years between 2013 and 2015.

Maternal age/date of birth was recorded for only 286 patients. The youngest gave birth to a DS child at 16 years of age, while the oldest was aged 53 years (Figures 2,3). The mean maternal age in the whole group was found to be 34.5 years [95% CI: 33.7- 35.3]. In total, 46.85% were aged 34 and below, 44.4% were between 30 and 39 years, while 27.27% were aged between 40 and 53 years. When calculated only for those with free trisomy 21 DS (276 patients), the mean maternal age is 34.6 years [95% CI: 33.8-35.5].

Using the Wilcoxon signed-rank test, the z test statistic calculated at the median maternal age of 26.3 years was 12.9 [$p > |z| = 0.0000$ or p value < 0.0001] for those patients with free trisomy 21 DS; positive and negative observations were 233 and 43, respectively. Similar findings were obtained when comparison was made to the median maternal for the last-born; the z test statistic was 10.3 [$p > |z| = 0.0000$ or p value < 0.0001], while positive and negative observations were 200 and 76, respectively.

DS continues to be the most common identified genetic conditions in Rwanda as it is the case worldwide[1,11,17]. The average number has increased overtime since the beginning of genetic services with now 35 patients per year (320 patients over

Table 1 A: Karyotype results[i]

Karyotype	Freq.	Percent	Cum.
47, XY, +21	157	49.06	49.06
47, XX, +21	151	47.19	96.25
46, XY, rob t(21;21)(q10;q10)	3	0.94	97.19
46, XX, rob t(21;21)(q10;q10)	3	0.94	98.13
Other	6	1.88	100
Total	320	100	440.63

Abbreviations: rob t = Robertsonian Translocation
[i]One patient with double trisomy 48, XXX, +21 was intentionally registered as 47, XX + 21 for statistical purposes

Table 1 B: Other karyotype results.

Other karyotypes	Freq.	Percent	Cum.
46 , X, der (Y) t (Y,21) (q11.21,q11.2)	1	14.29	14.29
46, XX, rob t (21;22) (q10;q10)	2	28.57	42.86
46, XX, t (14;21) (q10.q10)	1	14.29	57.14
46, XY, t (15;21) (q10.q10)	1	14.29	71.43
47, XY t (13;21) (q10;q10)	1	14.29	85.71
47, XY, + 21 inv9 (p11;q13)	1	14.29	100
Total	7	100	371.43

Abbreviations: der = Derivative Chromosome; t: Translocation

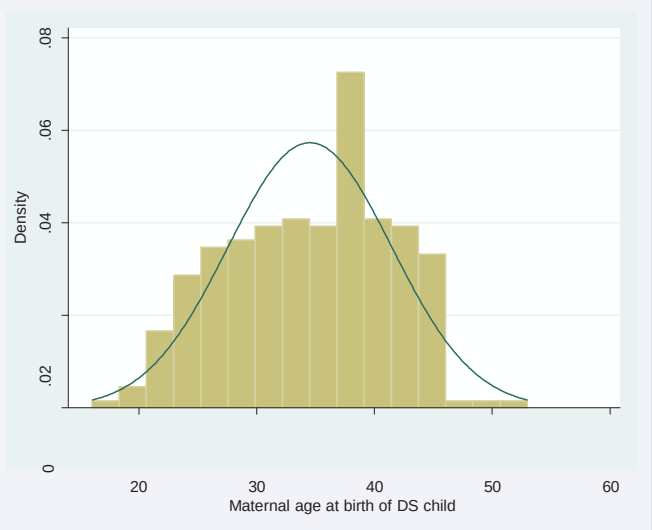

Figure 2 Maternal age distribution curve.

9 years and 3 months) while it was 22 patients per year in 2010. This probably results from increasing awareness of medical professionals and population. Findings of this study showed that large proportion (53.15%) of infants with DS diagnosed in Rwanda were born to mothers with advanced age (35 years old and above) and statistically the maternal age for these children was significantly higher than the maternal age at childbirth in the Rwanda general population [*p* value < 0.0001].

These results differ from those found earlier in 2007 at the same center [13]; the mean maternal age was 31.6 years in the 2007 study while it was 34.5 years for the current one [for all the types of DS karyotypes, and not for standard trisomy alone]; while the mothers 34 years and younger represented 72.4% in 2007, we found only 46.8% in this study. These findings differ largely because the sample size was much smaller in 2007 than in the current study (29 mothers in 2007 *vs* 286 mothers today). Similarly, our current findings contrast with some other previous studies like in India where majority of DS infants were born to mothers aged below 35 years [9,10]; these 2 Indian studies showed large proportions of mothers aged less 35 years with 92.7% (or 64/69) and 85% (or 250/294) respectively. The sample size in the latter study is very similar to ours *i.e.* 294 *vs* 286 mothers though the 2 populations are quite different with respect to race,cultural and other social demographic aspects. However, the percentage of mothers aged below 35 years (85%) is much higher than what we found in our study (46.85%); the author did not do any comparison with a control to make inferential statistics but simply described the significant statistical difference between the 2 maternal age ranges (below 35 years and ≥ 35 years) with regard to the occurrence births (X^2 = 1.22 and p value= 0.002). According to another Indian study with 69 cases of Down syndrome, the researchers managed to conduct a comparative analysis with a control from 200 families selected randomly from the same community, and they studied both parents and grandparents. Though the study was of small sample compared to ours, the authors found that in both cases and control, more children were born to young mothers; 75% of DS cases were born to mothers aged between 18 and 29 years, and in the control more children were born to young mothers (18-24 years) and father of advanced age (30-35 years). The authors thought it could be due to the fact that usually Indian women get married at young age. Interestingly, in the same study, the authors found that the advanced maternal grandmother age was a risk factor for DS births. In their multiple logistic regression model, only grandmother' age showed a significant difference in the odds ratios among the 4 variables (consanguineous marriage and ages of mother, father and maternal grandmother) analyzed: OR= 1.30, 95% CI 1.22; 1.39 and p value < 0.001. Most our data were obtained retrospectively and information about the age of maternal grandmothers and fathers were missing and their effect on the occurrence of DS could not be analyzed.

Our study would compare best with others in our region

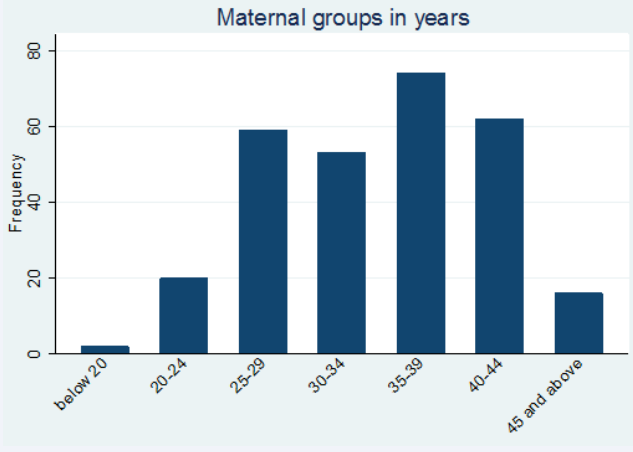

Figure 3 Age groups for mothers of DS patients.

where population presents similarities at least for race (black) and close cultures but there are almost no data. Nevertheless, the proportion of advanced maternal age in our study was comparable to findings in South African hospital-based birth prevalence studies; in Pretoria urban academic hospital, a rural hospital and Johannesburg academic hospital studies, DS infants born to mothers aged 35 years and above were 52%, 56% and 55%, respectively [18]. Similarly in the 20-year birth prevalence study in Cape Town, from available data on maternal age between years 1987 and 1993, DS infants born to mothers aged over 35 years were 35%, 52% and 60% for whites, colored and blacks respectively. Here, the researchers confirmed the increasing risk for DS with advancing maternal age and there was no significant difference in birth prevalence in the three race groups [19]. In this study, the number of mothers with known age (from 1987 to 1993) was 261 and similar to our sample size; again the researchers were interested in birth incidence/prevalence and no inference in the general population was made. In the 2012 annual report in England and wales, the mean age for women at birth of their infants with a postnatal diagnosis of Down syndrome was 35.3 (95% CI: 34.8 – 35.9), with an overall (pre and postnatally diagnosed) 65% or 1163/1786 of the women aged 35 or older [20]; these results are comparable/consistent with our current findings. Similar results were found in other European countries from EUROCAT (European Surveillance of Congenital Anomalies) registries over 20 years between 1990 and 2009 [21]; over half of DS cases occurred in mothers aged 35 years and above in 10 of the 12 participating European countries (Table 2).

Whether studies mentioned above compare well or not our findings, this has given us a different trend from what we believed before (or at least from the few data we had) in maternal age vis-à-vis the occurrence of DS syndrome births in Rwanda. If we found similar results *i.e.* DS infants being born more to younger mothers, our future researches would focus on determining other etiologic risk factors like those stipulated in literature [3,7,8] and would recommend other policies like prenatal screening and diagnosis to consider and base on that situation.

The mean age at which the diagnosis of DS was confirmed with a karyotype (20.5 months) was markedly lower in this study compared to that in the 2007 study at the same center (9.2 years) [13]. Again, this may partly result from improved awareness of medical care providers vis-à-vis Down syndrome and use of genetic services which may explain a big percentage (>50%) of cases diagnosed only over the last 3 years of the considered period of more than 9 years; another possible contributing factor was an improved use of health care services in general thanks to the community based health insurance as it was evidenced by the large proportion of its holders in this study (72.8% or 190/261 known insured patients). The existing transfer system also allows for patients from any corner in the country to reach referral hospitals where genetic services are available, but it is likely that number of patients may fail to consult given different social economic reasons especially for those from remote areas.

DS morbidity and mortality associated social-economic and financial expenses are a big burden for both patients' families and the country and deserve a special attention for the optimal care of affected individuals from early infancy to adult life. A big challenge with these patients is access to corrective surgery for congenital heart defects (CHDs) affecting around half of DS infants. In our study, 172 patients (53.7%) had echocardiography done and 113 of them (65.7%) had abnormal anatomical findings or congenital defects. These figures were much higher than what it is already known from other studies because it is possible that those with suspected heart defects from physical exam were more likely to have echocardiography requested, and no systematic screening of heart defects was done; if they are taken from the total group (i.e. 113/320 or 35.3%), it may underestimate the magnitude of the problem. In any case we may say with some certainty that CHDs frequency ranges from 35.3% to 65.7% in our studied population of patients with DS, which confirms, like in other researches that CHDs are a major birth defect among the Down's. The prevalence of CHDs in Rwanda is not known but this seems to be very important and DS is by far the known genetic disorder identified to be associated with these congenital anomalies in the Rwandan children as demonstrated in our previous study [22]. Today cardiac surgery is possible in Rwanda thanks to visiting teams from Australia, Belgium or the United States of America coming twice a year on average; there is always a long waiting list and only from those considered to have a "good prognosis" are selected patients to benefit from surgery. DS syndrome patients are not part of priority in these programs and are almost totally excluded. To the best of our knowledge and from the families we have maintained a regular follow-up, only five patients benefited from cardiovascular surgery and three of them had to go out of Africa (1 infant underwent open heart surgery in Germany, the second one in India, and the 3rd in the USA); 2 children had their surgery at King Faisal Hospital, Rwanda (one underwent a PDA closure, the 2nd had open heart surgery). Another family reported their child died while they were in process to take him abroad for heart surgery. Other associated birth defects were reported for 10 patients only. Four patients had gastrointestinal tube-related disorders (1 case of imperforate anus, 2 cases of Hirschsprung disease, 1 case of duodenal atresia), 1 patient had congenital cataract, 2 patients had urinary tract disorders (cryptorchidism and hypospadias, 1 anomaly for each patient), and hypothyroidism (not clear whether congenital or acquired), hydrocephalus and brachial cleft cyst were documented for 1 patient respectively. These disorders and others are probably underreported or simply overlooked since there no systematic

Table 2: Number of Down syndrome patients diagnosed in different years.

Year of test	Freq.	Percent	Cum
2007	18	5.63	5.63
2008	10	3.13	8.75
2009	13	4.06	12.81
2010	57	17.81	30.63
2011	33	10.31	40.94
2012	21	6.56	47.5
2013	35	10.94	58.44
2014	47	14.69	73.13
2015	79	24.69	97.81
2016	7	2.19	100
Total	320	100	475.64

screening for their detection which shows the need to build a well organized and strong multidisciplinary approach for the management and follow-up of this vulnerable group of patients as well as the improvement in documentation of health system of the country in general.

The incidence and/or prevalence of DS births are likely to change since initiatives for specific surveillance programs are being undertaken in Rwanda and also due to the awareness of the authorities and families. In developed world, majority of DS cases are prenatally diagnosed and are likely to result in termination of pregnancy for fetal anomalies ≥ 80% for (EUROCAT registries) where this practice is legally accepted [17,18]. This has prevented the live birth prevalence of DS from increasing as the number of affected pregnancies has increased due to the rise in average of maternal age [18]. Thus, with an increasing awareness of the general public, prenatal diagnosis is going to be inevitably more and more demanded in Rwanda. The medical professionals, especially obstetricians have to get prepared and think of setting up required equipment and technical expertise. Though advanced maternal age was (in our study and many others done before) an important major risk factor for DS pregnancies, there is always a big proportion of children born to young mothers for which risk factors are yet to be determined. If prenatal diagnosis services were started in Rwanda, their offer would not simply base on advanced maternal age as lonely criterion as it is no longer the case in developed world with a similar trend in maternal age for DS births.

In conclusion, DS is an important problem and deserves a special attention in Rwanda. Our findings showed that DS infants are born to more aged mothers than others in general population, a trend similar to that observed in developed world. Prenatal diagnosis is urgently needed to respond to a high demand likely to occur in a near future. And more organized, multidisciplinary and patient/family-centered approach is yet to be achieved for optimal management of those infants born with the condition.

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REFERENCES

1. Dey SK, Ghosh. Risk of Etiology Advanced of Down Maternal Syndrome Age and Altered Meiotic Recombination for Chromosome 21 Non disjunction. In: Genetics and Etiology of Down syndrome. 2011. 1-38.
2. Warren AC, Chakravarti A, Wong C, Slaugenhaupt SA, Halloran SL, Watkins PC, et al. Evidence for reduced recombination on the non disjoined chromosomes 21 in Down syndrome. Science. 1987; 237: 652-654.
3. Sherman SL, Freeman SB, Allen EG, Lamb NE. Risk factors for non disjunction of trisomy 21. Cytogenet Genome Res. 2005; 111: 273-280.
4. Harris RA, Washington AE, Nease RF, Kuppermann M. Cost utility of prenatal diagnosis and the risk-based threshold. Lancet. 2004; 363: 276-282.
5. Berkowitz RL, Roberts J, Minkoff H. Challenging the strategy of maternal age-based prenatal genetic counseling. JAMA. 2006; 295: 1446-1448.
6. Oliver TR, Bhise A, Feingold E, Tinker S, Masse N, Sherman SL. Investigation of factors associated with paternal non disjunction of chromosome 21. Am J Med Genet A. 2009; 149: 1685-1690.
7. Cuckle HS. Primary prevention of Down's syndrome. Int J Med Sci. 2005; 2: 93-99.
8. Patterson D. Folate metabolism and the risk of Down syndrome. Downs Syndr Res Pract. 2008; 12: 93-97.
9. Malini SS, Ramachandra NB. Influence of advanced age of maternal grandmothers on Down syndrome. BMC Med Genet. 2006; 7: 4.
10. Tajeddini R. A Retrospective Study on Maternal Age and Down syndrome. Int J Humanit Soc Sci Invent. 2011; 2: 13–18.
11. Oloyede OA. Down syndrome in Nigeria Sub Saharan Africa. Prenat diagnosis Screen Down Syndr. 2011; 165–76.
12. Mutesa L, Uwineza A, Hellin AC, Muvunyi CM, Vanbellinghen JF, Umurerwa L, et al. A Survey of Genetic Diseases in Rwanda. Rwanda Med Journaledical J. 2010; 68: 1-13.
13. Mutesa L, Muganga N, Pierquin G. Clinical and Cytogenetic Profile of Down Syndrome in Rwandan Patients. Interest of prenatal diagnosis. Rwanda Med J. 2007; 66: 5–10.
14. NISR (National Institute of Statistics of Rwanda). Ministry of Finance and Economic Planning (MINECOFIN). Rwanda Fourth Population and Housing Census 2012. NISR. 2014.
15. NISR (National Institute of Statistics of Rwanda). MOH (Ministry of Health). Rwanda Demographic and Health Survey 2010. 2012.
16. NISR (National Institute of Statistics of Rwanda) MOH (Ministry of Health) [Rwanda]. ICF International. Rwanda Demographic and Health Survey 2014-15: 2015.
17. Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. Ment Retard Dev Disabil Res Rev. 2007; 13: 221-227.
18. Christianson AL. Down syndrome in sub-Saharan Africa. J Med Genet. 1996; 33: 89-92.
19. Molteno C, Smart R, Viljoen D, Sayed R, Roux A. Twenty-year birth prevalence of Down syndrome in Cape Town , South Africa. Paediatr Perinat Epidemiol. 1997; 11: 428–35.
20. Morris JK, Springett A, Morris J, Clancy E, Springett A. The National Down Syndrome Cytogenetic: 2012 Annual Register for England and Wales report. 2014; 0–31.
21. Loane M, Morris JK, Addor M, Arriola L, Budd J, Doray B, et al. Twenty-year trends in the prevalence: impact of Down syndrome and other trisomies in Europe of maternal age and prenatal screening. Eur J Hum Genet. 2013; 21: 27-33.
22. Teteli R, Uwineza A, Butera Y, Hitayezu J, Murorunkwere S, Umurerwa L, et al. Pattern of congenital heart diseases in Rwandan children with genetic defects. Pan Afr Med J. 2014; 19: 85.

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