JOGM
Journal of Global Medicine

REVIEW ARTICLE

Prenatal diagnosis and preimplantation genetic diagnosis for sickle cell disease in Africa

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Abstract

Sickle cell disease (SCD) is the most common genetic haematological disorder worldwide, and it is a major public health concern, especially in Sub-Saharan Africa. Prenatal diagnosis (PD) and preimplantation genetic diagnosis (PGD) are important reproductive options for the prevention of SCD. Despite the high prevalence of SCD in Nigeria and Sub-Saharan Africa, current trends in PD and PGD for the prevention of SCD are still slow compared to that in developed countries. Attitudes towards PD and PGD for the prevention of SCD in African are influenced by level of awareness, knowledge and educational status, and the main barriers to the uptake of PD and PGD for SCD in Africa are cost, religion, sociocultural, ethical and moral considerations. We reviewed available data on PD and PGD for SCD in Africa, using the PubMed, PubMed Central, Google Scholar and African Index Medicus search engines, through a combination of words and phrases relevant to the subject. This article reviewed the current trends in PD and PGD for the prevention of SCD and discussed the attitudes towards and the barriers to the uptake of PD and PGD for SCD in Africa.

Keywords: *preimplantation genetic diagnosis*; *prenatal diagnosis*; *sickle cell disease*; *in vitro fertilization*; *chorionic villus sampling*; *amniocentesis*

Received: 23 October 2022; Accepted: 3 December 2022; Published: 8 February 2023

Prenatal diagnosis (PD) and preimplantation genetic diagnosis (PGD) represent highly important reproductive choices for couples with a high risk of transmitting a severe genetic disorder but who wish to have a healthy family [1]. Sickle cell disease (SCD) is the commonest genetic disorder in Sub-Saharan Africa [2]. SCD refers to a group of conditions characterized by the presence of haemoglobin S (HbS) and one other abnormal haemoglobin [3]. And the two commonest haemoglobin variants reported in Nigeria are HbS and haemoglobin C (HbC) [4]. SCD remains a major cause of mortality and morbidity in Nigeria, a country with the highest burden of the disease both in Africa and the world [4].

Globally, about 50 million people are living with SCD, and Nigeria remains the epicentre zone with about 4–6 million people living with the disease (one in every four Nigerians has a sickle cell trait) [5]. Worldwide, about 300,000 newly diagnosed SCD children are born annually, and Sub-Saharan Africa contributes about 75% of the number. And Nigeria contributes 33% of the global burden of SCD [5]. The high burden of SCD in Africa has been attributed to the survival advantage conferred by sickle cell trait against the malaria parasite (*Plasmodium falciparum*) [6]. Despite the enormous burden of SCD particularly in Nigeria and Sub-Saharan Africa, the uptake and application of PD and PGD for SCD in this region are low [6]. And little has changed in Nigeria as regards recent advances in the management of this disorder, as genetic screening using PD and PGD is not readily accessible in Nigeria [4].

PD refers to the use of techniques to detect the presence or absence of foetal abnormalities [6]. In the context of SCD, PD will detect the haemoglobin genotype of the foetus, hence giving the couple room to prepare themselves for the birth of the child or to terminate the pregnancy [6]. PD for SCD can be done through two major techniques, chorionic villus sampling (CVS) and amniocentesis are as shown in Figure 1 and Figure 2 respectively [7]. Though CVS (done at 10 to 12 weeks of gestation and DNA analysis) remains the method of choice, sometimes, at-risk couples can still be offered amniocentesis at 14–15 weeks gestation and DNA analysis when identified late in the second trimester [7]. Newer methods of PD that are non-invasive are done by isolating foetal cells from maternal blood for DNA analysis [8]. Other techniques include cordocentesis for foetal blood sampling and DNA analysis at 18–19 weeks gestation, and celocentesis, where the celomic fluid is

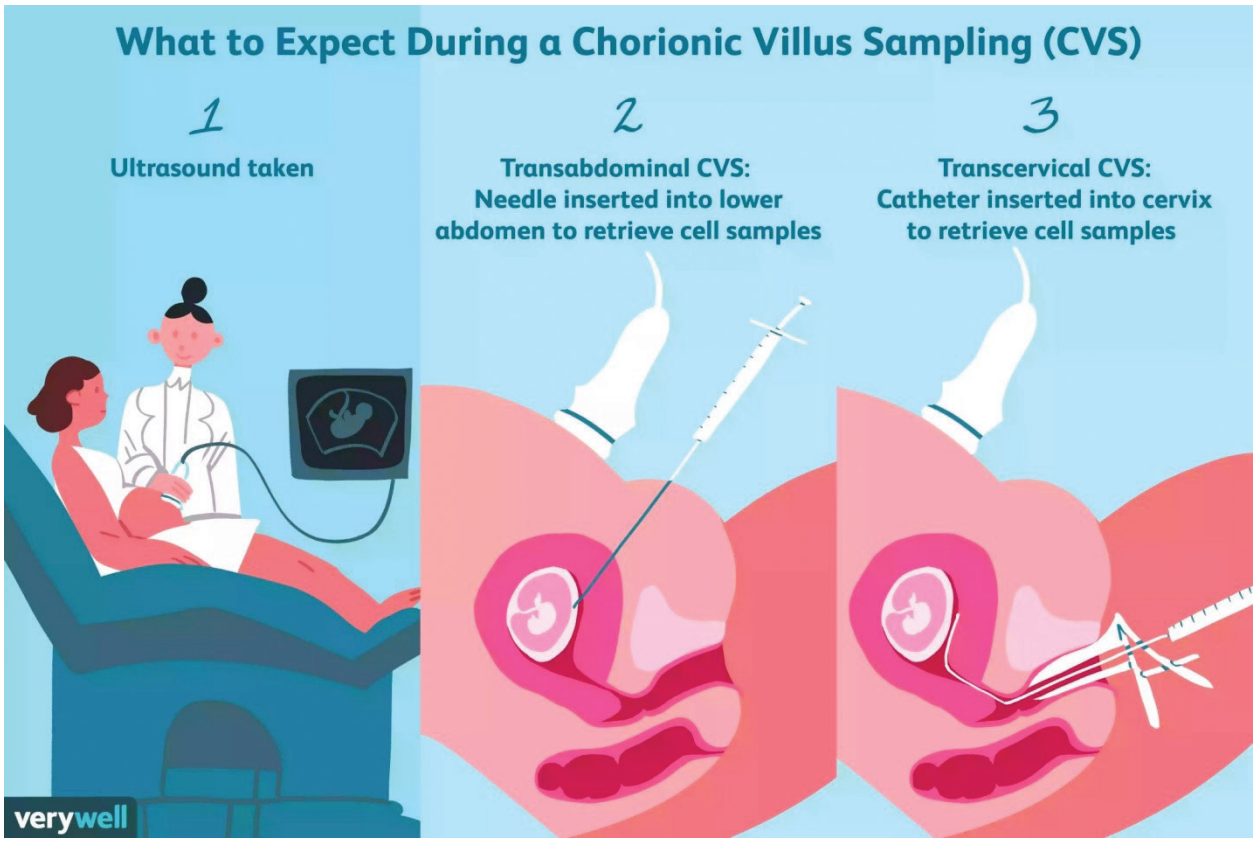

Fig. 1. Step for chorionic villus sampling.

aspirated at 7–9 weeks gestation [8]. The major disadvantage with the invasive PD is the risk of miscarriage, and there is potentially a need for the termination of an affected pregnancy [7].

PGD is an evolving technique that provides a practical alternative to PD and termination of pregnancy for couples who are at substantial risk of transmitting SCD to their offspring [9]. Samples for genetic testing are obtained from oocytes or cleaving embryos after in vitro fertilization [10]. Only embryos that are shown to be free of the genetic disorders are made available for replacement in the uterus, in the hope of establishing a pregnancy [11]. A PGD cycle entails an ovarian stimulation, oocyte fertilization by In vitro fertilization (IVF), embryo culture, embryo biopsy, genetic analysis and embryo transfer to the uterus as shown in Figure 3 [12]. Three types of biopsies may be used for PGD: polar body biopsy, cleavage stage biopsy and blastocyst stage biopsy [10]. PGD has provided unique insights into aspects of reproductive genetics and early human development [11] but is limited by the need to involve assisted reproduction, even in couples without fertility problems [13]. Furthermore, even for fertile couples, pregnancy rates rarely surpass 30–35% [4]. PGD has also raised important new ethical issues about assisted human reproduction [11].

The awareness, uptake and applications of various types of PD and PGD for SCD have continued to increase but low in Africa. There is paucity of studies that examined the current trends, awareness, uptake and perceptions of PD and PGD for SCD in this region. Hence, this article reviewed the current trends in PD and PGD for the prevention of SCD and discussed the attitudes towards and the barriers to the uptake of PD and PGD for SCD in Africa.

Sickle cell disease

SCD remains the most common inherited haemoglobinopathy worldwide [14]. It arises from a single-nucleotide substitution that leads to a propensity towards haemoglobin polymerization and the sickling of red blood cells (RBC) [15]. SCD is the first molecular illness explained by a single point mutation (A!T) resulting in the replacement of valine for glutamic acid in the 6th amino acid on chromosome 11 [15]. SCD may be classified according to the number and types of the two alleles of beta-globin into homozygous HbSS (sickle cell anaemia), HbAS (sickle cell trait), compound heterozygous (HbSC, HbSD, HbSE and HbS-O Arab disease) and HbSβ thalassaemia (HbSβ-Thal) [16]. The geographical distribution of these Hb variants differs and often parallels certain attributes such as climatic conditions and malaria endemicity. While the

Citation: Journal of Global Medicine 2022, **2**: 75 - http://dx.doi.org/10.51496/jogm.v2.75

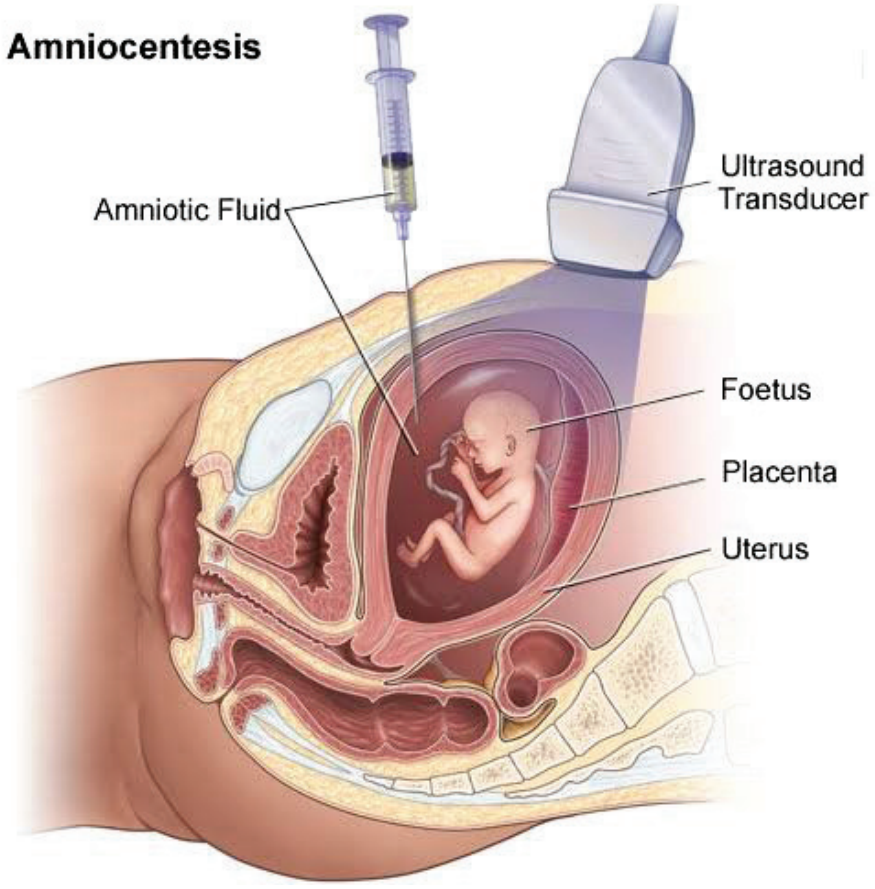

Fig. 2. Step for amniocentesis.

HbSS and HbSC diseases are highly prevalent in Sub-Saharan Africa, particularly West Africa, the HbSβ-Thal, HbSD and HbSE are more common in parts of the Middle East and Asia [17]. A person who inherits two abnormal (HbS) genes acquires the SCD (HbSS), and persons with one normal (HbA) and one abnormal (HbS) gene develop into sickle cell trait (HbAS) [14].

The chance of inheritance of sickle cell gene from parents to offspring is of five possibilities, and they are as follows: 1) If both parents (father and mother) are carrying a haemoglobin variant, that is, trait, there is one in four possibilities of the child inheriting both the abnormal genes therefore and having sickle cell anaemia. 2) The possibility rises to one in two, if one parent has the trait and other one parent has disease. 3) If one parent has trait and other is normal, there is a 50% possibility in every pregnancy to have a sickle cell trait. 4) If both parents have SCD, then each child will have SCD. 5) If one parent has SCD and another one normal, then each child will have sickle cell trait [14].

Genetic counselling

Prevention of SCD through carrier identification and genetic counselling (GC) remain the only realistic approach to reduce the impact of the disease and allow better use of available resources in low-income countries like Nigeria, where the condition is most prevalent [18]. GC forms an integral component of care or service offered to couples at risk. It is recommended that couples at risk should be counselled by a qualified health professional with special interest and well versed in the molecular diversity of the haemoglobinopathies [13]. In addition to genetic and psychological counselling done, the at-risk couple should be given detailed, accurate and comprehensive information for informed decision-making [6]. And this information should include indications for testing and the risks, benefits and limitations of both PD and PGD in detail and in a language understandable by the couples [6]. A couple at risk refers to a couple who are both healthy carriers of sickle cell trait (HbAS), one has the sickle cell trait (HbAS) and the other has HbAC trait, or one has sickle cell anaemia (HbSS) and the other has sickle cell trait (HbAS) [6]. And they should be informed of the options of PD and PGD.

Premarital screening and antenatal screening for haemoglobin genotype form a major component of prevention of SCD. In Nigeria, premarital GC is voluntary; however, premarital screening for the sickle cell gene is

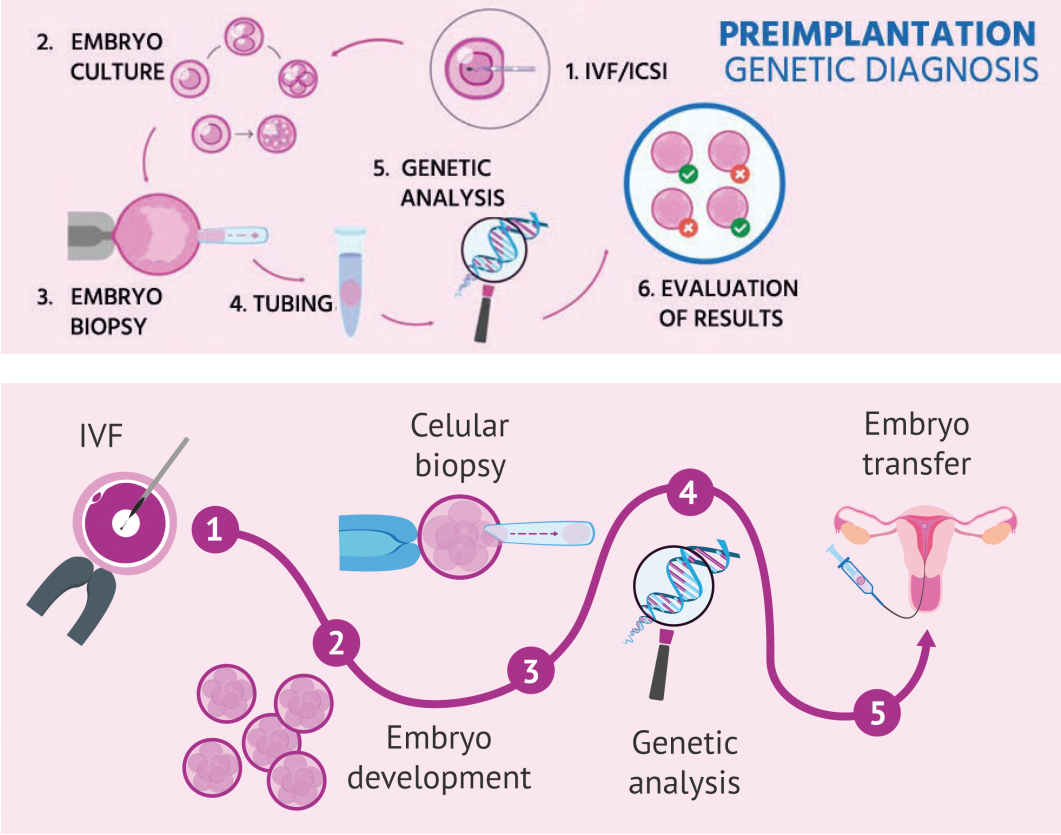

Fig. 3. Stages of preimplantation genetic diagnosis.

considered one of the methods of preventing new birth of children with SCD [19]. Premarital screening is fast gaining ground as a prerequisite for solemnization of holy matrimony by many faith-based organizations in Nigeria [20]. It forms the baseline assessment of prospective marriage couples with the aim of reducing genetic risk and incidence of babies born with SCD [20]. Antenatal screening for haemoglobin genotype is a component of routine antenatal investigations in Nigeria [21]. In both cases, haemoglobin electrophoresis is done, and the result is used to educate and counsel couple at risk for genetic screening with PGD or PD.

Prenatal diagnosis

PD is a reproductive option that provides parents with the option to test at-risk pregnancies and make decisions regarding affected pregnancies [22]. It remains an important option for couples at-risk of having a child with SCD. With increasing awareness in the community, more couples are opting for PD [23]. But this is not the case in Nigeria where the level of awareness is still low. The availability of non-invasive prenatal diagnosis (NIPD), which circumvents the need for invasive sampling and has no perceived procedure-related miscarriage risk, is predicted to increase the uptake of PD for SCD [24]. NIPD is done through the analysis of foetal cell-free DNA circulating in the maternal bloodstream, and this can be carried out from as early as 8 weeks. Though NIPD is not yet available for SCD, it has the potential to increase the uptake of prenatal testing for SCD [24]. The comparisons between current and emerging prenatal and preimplantation genetic diagnosis are as shown in Table 1.

Chioma et al. in South-south Nigeria observed that there is still a gap in knowledge and utilization of PD by at risk couples [6]. Ahmed et al. in North-western Nigeria observed that there was overall poor knowledge of PD among pregnant women attending antenatal clinic, and the level of education was a key identifiable factor that determined knowledge and acceptability of PD [25]. Ademosun et al. in South-western Nigeria reported that very few (20%) have adequate knowledge about PD as an existing control measure for sickle cell births [2]. Knowledge and acceptance of sickle cell control measures among pregnant women was hierarchically scaled as GC > PD > PGD in south-western Nigeria [2]. And this knowledge was not a determining factor in their perception or acceptance of the control measures [2]. Educational attainment, age, marital status and religion affect the acceptability of PD [26]. Perceptions of PD in Africa have been associated with issues on ethics concerning the termination of an ongoing sickle cell pregnancy. Majority would prefer pregnancy termination following

Citation: Journal of Global Medicine 2022, **2**: 75 - http://dx.doi.org/10.51496/jogm.v2.75

Table 1. Comparison between current and emerging prenatal and preimplantation genetic diagnostic procedures.

	Conventional PD	PGD	NIPD
Timing of genetic analysis	During pregnancy (from 11 weeks by CVS or from 15 weeks by amniocentesis)	Before initiation of pregnancy and embryo transfer (during ART)	From 8 weeks of pregnancy (by maternal blood draw)
Risk to foetus, pregnancy or baby	Miscarriage ~2% (rarely complications such as infection or foetal injury)	Same risk as associated with conventional ART	None
Accuracy of genetic analysis	>99%	>99%	Yet to be extensively validated
Chance of healthy delivery	75% (based on genetic risk according to autosomal recessive disease transmission)	30% per embryo transfer (liwmited by known rates of embryo implantation and pregnancy outcomes)	75% (based on genetic risk according to autosomal recessive disease transmission)
Major drawback(s)	Need to terminate affected pregnancy	Technically challenging, multi-step and labour-intensive	Need to terminate affected pregnancy
		Requires ART (even if couple fertile)	Extensive validation pending
		Unpredictable pregnancy and birth rate	
		Relatively costly	
Major benefit(s)	Well-validated procedure	Precludes need to terminate affected pregnancies	Early diagnosis
			Limited risks in pregnancy

a confirmation of sickle cell disorder after PD; most asserted that the trauma of having a sickle cell baby would be too much to bear [2].

The availability and acceptability of PD and termination of an affected pregnancy are of particular importance in low-resource countries, where neither health services nor families can afford to pay for long-term treatment of SCD [22]. Approximately 67% of a sample of 130 Cameroonian parents with affected children reported they would accept termination of an affected pregnancy for SCD, and this was considerably higher when compared to the Cameroonian preclinical and clinical medical students, and physicians in a previous study (22.4, 10.8 and 36.1%, respectively) [22]. In Nigeria, the trends reported were slightly different, where 92% of a sample of 53 SCD heterozygous carrier mothers favoured PD and 63% indicated they would opt for termination of an affected pregnancy [22]. However, in a survey of 403 health workers in a tertiary health care centre in Nigeria, only one-third of the respondents accepts termination of pregnancy as an option if prenatal screening is positive for SCD, whereas close to half of the respondents (42%) were against the idea. Another study reported that 21.4% of Nigerian doctors would accept termination of an affected pregnancy for SCD [27]. The views of parents towards PD and in some cases medical termination of pregnancy may be associated with their experience of affected patients and the psychosocial and/or economic impact of SCD on families.

Ethical issues arise in terms of the safety of the procedures used in obtaining tissue sample for PD, abortion of affected foetuses, the question of genetic selection, the ethical implications of GC and issues relating to the principle of justice in health care. The safety of the procedures used for PD is worth mentioning first. PD is relatively safe; however, there is a chance of a miscarriage following CVS and amniocentesis (worse with CVS and usually multi-factorial). Abortion of the affected foetus is regarded as a component of PD in most cases. In the case of the foetus having the SS genotype, the ethical question arises whether to have an abortion or to keep the pregnancy. The decision whether to terminate a pregnancy based on a positive result is usually a difficult one that involves religious, psychosocial and cultural considerations. There is also risk associated with carrying out an abortion, especially in developing country where there may be lack of reliable and safe healthcare practices [28].

Legal bans on abortion exist virtually in all African countries, and medical abortion when allowed is often restricted to direct threats to maternal health [29]. In all parts of Nigeria, abortion is a criminal offense except where it is performed to save the life of the mother [30]. In the South, the relevant provisions are sections 228, 229, 230, 297 and 328 of the Criminal Code [Criminal Code Act(1916) Cap]. In the North, the relevant provisions are sections 232, 233, 234, 235 and 236 of the Penal Code [Penal Code Act(1960) Cap] [30]. Foetal pathology like SCD is not considered, and abortion of affected foetuses would, therefore, be illegal [29].

Even when abortion is legal in the local context, the question of whether it is right to terminate an innocent life is still a much-debated issue. On the other hand, the question of whether it is right or not to bring a child with a disease condition that causes so much suffering to the

world when a decision is made to keep the pregnancy remained unresolved. Some would argue that it is more cost effective to abort the affected foetuses as this will reduce the socioeconomic and emotional consequences of the disease. Bringing up the question of cost-effectiveness and life of patients would be looked at in many developing countries like Nigeria as being cold and inhuman, but the reality of scarcity of resources and rationing of healthcare resources is there for all to see.

Some people would argue that using a PD for SCD would lead to a systematic elimination of genetic mutation from the population. Could this be called a form of eugenics? The authors do not think so as the choice here is not about specific traits that are desired in a child but having a child free of a particular genetic disorder. The right to know is a fundamental right of the couple; hence, carrying out a PD for SCD empowers the couple to plan for the new child (if they decide to keep the pregnancy – if SS genotype) and gives them peace of mind (if AS or AA genotype). This is the autonomous choice of the couple, a right to decide what is acceptable to them. There is also the risk of pressure being put on the couple directly or indirectly by society to have PD done because of the availability of the tests (the so-called technological imperative). This could lead to affected couples being blamed for not making use of the tests to avoid having children with SCD.

Preimplantation genetic diagnosis

PGD for the prevention of SCD is a recognized alternative to PD and termination of an affected pregnancy for at-risk couples [9]. PGD is a procedure for accurate genetic diagnosis, careful selection of unaffected embryo and implantation to allow fertile or infertile couples to have offspring without SCD [22]. PGD is not 100% accurate, and the most common form of PGD involves the extraction of one or two cells from the preimplantation embryo, often around the 8-cell stage [31]. PGD costs about 4–6.5 million naira (6–10,000 US$). In Nigeria, the first unaffected pregnancy and delivery after a successful PGD for SCD was reported in 2014 [31].

The prevalence of HbS gene is high in Nigeria and Sub-Saharan Africa, but access to PGD services in the region is limited [32]. This is because of the required technological expertise and the high healthcare costs associated with IVF [33]. In the United Kingdom (UK), couples who are at risk of having a child affected with SCD and have no unaffected children are entitled to a maximum of three state-funded PGD cycles, and this has improved the uptake of PGD for SCD in the UK [9] as compared to Nigeria, where it is personally funded. The principle of justice in health care requires that access to PGD be fair and equitable. This is not so because of intra-country and inter-country disparity in access to PGD; many people requiring this technology for SCD may not have access to it because of lack of the service in their environment or inability to pay for the services. This is particularly common in developing countries of Sub-Saharan Africa where payment for health care is still mainly 'out of pocket' [34]. This problem of access to PGD remains one of the major barriers to the control of SCD in developing countries.

PGD requires close collaboration between fertility specialists, molecular biologists, geneticists, and genetic and fertility counsellors and may be an option to individuals who may object to PD followed by termination [22]. In Nigeria, in-vitro fertilization centres rely on collaboration with genetic laboratories in high-income countries for PGD [32]. The awareness and the uptake of PGD for SCD in Nigeria and Sub-Saharan Africa are still poor. Recent advances in PGD technology, such as small-volume biopsy techniques, have improved embryo safety, diagnostic accuracy and cost effectiveness of PGD. Furthermore, single-cell genomic and non-invasive sampling techniques are currently in development, which promise to further improve diagnostics and reduce potential ethical concerns [35].

The introduction of PGD in developed countries would seem to have put the controversial issue of termination of affected pregnancy at rest as only 'genetically healthy' embryos will be transferred to the uterus. However, PGD is also laden with its own concerns and ethical dilemmas relating to the moral status and destruction of embryos, and tendencies for eugenic practices. These concerns include the expensive nature of the procedure; burdensome procedure that is not entirely without risk for the woman; necessary embryo biopsy adding to the manipulation of gametes and embryos involved in IVF making PGD more invasive and creating many embryos that may eventually be discarded [36].

Finally, PGD is considered as ethically sensitive because, like selective abortion following PD, it amounts to a form of selective reproduction, in which only children not affected by SCD are allowed to be born. Some find this problematic holding that it would entail a discriminatory message about the worth of the lives of people living with SCD [36]. Others are concerned that allowing the selection of healthy embryos in vitro could be a first or a further step on a slippery slope towards the dreaded 'designer child' scenario, involving selection for non-health related characteristics as well.

Conclusion

Despite the high prevalence of SCD in Nigeria and Sub-Saharan Africa, current trends in PD and PGD for the prevention of SCD are still slow compared to that in developed countries. Attitudes towards PD and PGD for the prevention of SCD in African are influenced by level

Citation: Journal of Global Medicine 2022, 2: 75 - http://dx.doi.org/10.51496/jogm.v2.75

of awareness, knowledge and educational status, and the main barriers to the uptake of PD and PGD for SCD in Africa were cost; religion; safety; sociocultural, ethical and moral issues of genetic selection; destruction of embryos; and principles of justice. This not only will adversely affect health policy planning but also could, in addition, continue to fuel the already high prevalence of SCD in Africa, with attendant high morbidity and mortality in individuals born with the disease.

Conflict of interest and funding

The authors received no funding from any profit or non-profit organization for the research. There are no conflicts of interest.

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Citation: Journal of Global Medicine 2022, **2**: 75 - http://dx.doi.org/10.51496/jogm.v2.75