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Safe Marriage and Sperm Immobilization for Prevention of Genetically Inherited Disease

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Abstract

Genetic diseases devastate the society. Out of 9 million birth defects 7.9 are due to genetic causes. Management of most of the inherited disorders are very expensive and not affordable to majority. Early detection and lifelong therapy is mandatory. Palliative nature of the treatments available prolongs lives resulting in accumulation of cases and cost escalation. Therefore prevention is mandatory where the main focus would be detection of carriers of the defective genes. However most of the prevention methods available are not readily accessible or not acceptable due to inevitable financial constrains or self-imposed social cultural and religious reasons to majority. Therefore exploration of innovative approaches that goes beyond traditional recommendations is worthy considerations. "Safe marriage; avoidance of marriage between carriers by ensuring one of the partner in a couple to be a non-carrier suggest a practical no cost approach of prevention of recessively inherited disorders. The vision of safe marriage can extend to safe conception. For a safe marriage a non-carrier is selected from the society, for a safe conception a heterozygote father could provide millions of healthy sperms to be selected for conception. The author suggests using the advances of genetic sciences to explore the possibilities of selecting healthy sperms of immobilizing defective sperms and developing a vaginal jelly so that prevention of recessively inherited diseases becomes practical.

Introduction

Genetically inherited diseases are common problem. They are a universal global problem even though low and middle-income countries are more affected than the rest of the world. Out of 9 million babies born with severe form of a birth defect, 7.9 million babies have genetic origin for their defect [1]. At least 3.3 million children succumb within the first five years of life and 3.2 million have lifelong disability. Low and middle-income countries carry 94% of the total disease burden caused by birth defects and 95% of deaths due to birth defects [1]. Genetic defects contribute for diseases in 53/1000 people out of which single gene disorders contribute for 3.6/1000 cases, out of which 1.4/1000 are autosomal dominant, 1.7/1000 autosomal recessive and 0.5/1000 due to X linked disorders [2]. Haemoglobinopathies are the commonest monogenic disorder. Seven per cent of the world population carry defective genes, producing 300,000 – 400,000 babies with a severe disease every year [3].

Management is Costly

Managements of genetically inherited diseases are palliative, expensive and cumbersome. Cost of care varies from country to country depending on the level of care offered to particular patients. Cost of care for thalassaemia patients has been calculated in various settings. Karnon et al has reported lifetime cost of 830 002 American dollars (US$) in 1999 [4] but subsequent reports estimate the lifetime cost at US$ 1.8 million [5]. Reported cost of care for thalassaemia vary, Israel 1,971,380 US$ (5) UK 1,245,030 US$ [6] Canada 1,970,000 US$ [7] Thailand 7,604 $ per year [8]. As most of the treatment modalities are palliative, accumulation of the caseload is inevitable and countries will have to face escalation of costs [9]. Situation is even worse for other genetic disorders. Estimated lifetime cost of management varies according to the disease. Management of type one Gaucher disease for a life time will cost 5,716,473 euros [10] whereas life time cost of care for Pompe disses is 7 million euro [11], and same for Fabry disease is 7.9 – 8.8 million euro [12]. These circumstances made prevention a necessity rather than an option.

Prevention of Genetically Inherited Disorders

Available options for prevention are not acceptable to all nations and even to for all the carriers. This phenomenon is not only due to financial and technical constraints, but also due to self-imposed socio-religious and cultural barriers.

Prevention of genetically inherited diseases relies on carrier detection, especially when the conduction is autosomal recessive. In such situations screening of entire populations using affordable, acceptable and cost-effective methods should be utilized [13]. The problem of the asymptomatic carriers should be addressed with empathy to avoid stigmatisation and social problems that may crop up due to population screening. Traditionally the screening test is expected to be 100% sensitive. In screening for thalassaemia mean corpuscular volume (MCV) and mean corpuscular haemoglobin content (MCH) have a sensitivity of almost over 95%. However, the concerns remain regarding the possibility of missing some of E Beta thalassemia carriers by using these parameters only. Yet for all that, the positive impact of screening on the population should be weighed against the impact of missing a few cases on the society. Therefore it is high time to re-think about the need for 100% sensitive screening tests. In fact Jungner's principles pay attention to suitability, acceptability and cost-effectiveness more than its sensitivity [13].

What are the Options Available for Carriers of a Genetically Inherited Disease?

Antenatal diagnosis and abortion of affected foetuses

Pre-implantation diagnosis and selecting healthy foetuses

Gene therapy

Avoiding at-risk marriages

Artificial insemination from a healthy sperm donor

Adoption of a child

Promoting safe marriages

Using sperm immobilization jelly

First three options demand advanced technology and are not accessible to a majority in the world. However 4th to 6th options does not involve any cost but may be unconvincing for a civilized society. Safe marriage and adoption could be presented as a reasonable social intervention. Adoption would be considered as an option for failure. Implementing the concept of safe marriage is a mammoth task for sociologists and politicians. Sperm immobilization is a challenge for scientists involving molecular genetics.

Antenatal Diagnosis and Abortion of Affected Foetuses

Antenatal diagnosis and abortion of affected foetuses is the most commonly practiced method of prevention of genetically inherited diseases that has been successful in prevention of thalassaemia in Cyprus [14] Italy [15] Greece and UK [16]. The approach involves detecting at risk couples by screening for carrier status and offering antennal genetic diagnosis by chorionic villi biopsy or amniocentesis with the objective of aborting affected babies. The method has become popular in spite of the risk of abortion of the even a healthy foetus due to the procedure. Detection of at risk couples before conception facilitates the counselling process. In Cyprus availability of antenatal diagnosis since 1977 reduced the incidence of thalassaemia down to 18 cases as opposed to 77 which was the number expected without an intervention [14] and incidence of thalassaemia has come down to almost zero (16)

Pre Implantation Genetic Diagnosis

Pre-implantation genetic diagnosis and selecting a healthy foetus to deposit in the mother's womb is an ideal method for at risk couples who are not willing to abort a foetus for religious of social reasons [17]. In-vitro fertilization of harvested ovum is done by intra cytoplasmic insertion of sperms and 5th or 6th days after conception one or two cells from the 6-8 cell embryo is taken for genetic testing [17,18], that has been made possible on such a small sample due to the advent of polymerase chain reaction and fluorescence in-situ hybridization technique [18]. Testing the polar body of the ovum is a possibility to identify the healthy ovum even before in-vitro fertilization. However this would be useful only in cases of maternally derived disorders and some of the autosomal recessive diseases [18].

Gene Therapy

Gene therapy is evolving rapidly. Target of gene therapy include cancer, monogenic disorders and cardiovascular disorders. Viral vectors such as retroviral and adenoviral vectors and non-viral vectors such as plasmid have been tried. Numbers of trials are growing. By 2004, 24 countries report 918 trials, majority being from the USA [19]. By 2007, over 1340 clinical trails have been reported and out of them 32 has reached phase III [20]. In 2012 over 1800, gene therapy trials have been completed [21]. The therapeutic agent, Gendicine an adenovirus carrying the P53 gene to treat cancer has been used to treat more than 4000 patients even before the phase 3 trials, with reported successes of tumour suppression in China [20]. Trails for human gene transfer has been approved for over 25 monogenic disorders, 10 cardiovascular disorders, 9 infectious diseases, cancer involving many systems in the body, neurological, ocular and many other conditions [20]. Progress of gene therapy is compounded by failures leading to termination of some of the trials and even to pay compensations for patients [20].

Pre-marriage Counselling

Avoiding at-risk marriages is a sensible option in situations where antenatal diagnosis and abortions are not possible as a result of non-acceptance due sociocultural reasons, legal problems or non-availability of technical advances. Pre marriage counselling of at-risk couples had been practiced in Iran with the reduction of the number of new cases from 480 in 1998 to 78 cases in 2002 [22]. Thalassaemia prevention programme in Iran adopted a policy of screening couples at the time of registration for marriage by performing red cell indices on male partner of the prospective couple. If the male partner has mean corpuscular volume (MCV) more than 80 fl or mean corpuscular haemoglobin content (MCHC) more than 27 pg, the marriage was considered safe and advised to proceed with no further evaluations [22] However, if the male partner has MCV less than 80 fl or MCHC less than 27 pg, the female partner is also tested by FBC and if she has MCV above 80 fl and MCHC above 27 pg the marriage would be considered safe and the couple would be advised to proceed. However if both partners have MCV less than 80 fl or MCHC less than 27 pg further confirmation would be done with analysis of Haemoglobin A2 (HbA2) levels by High Performance Liquid Chromatography (HPLC). If the HbA2 levels are above 3.5%, thalassemia carrier status would be confirmed and the couple would be counselled by explaining the consequences of such a marriage. Over a period of 4 years 2.7 million prospective couples have been evaluated and 10,298 at risk couples have been identified. Half of such at-risk couples had given up the marriage contributing to a 50% reduction of incidence. Limiting the family size by informed couples is expected to contribute to a further reduction in incidence up to a level as low as 30% from the expected incidence [22]. The programme was economically viable as it utilized the existing health care facilities and respected the social beliefs and expectations and finally creating opportunities to introduce more advanced methods of prevention. However restrictions for abortions have been lifted in 1997 and a successful nationwide screening, counselling and pre-natal diagnosis (PND) programme has been launched [23].

Artificial Insemination from a Healthy Sperm Donor

This is not an option widely discussed. However anecdotal reports suggest the possibility of this practice. However there are no reports about this option in the literature, probably due to surreptitious nature of performing this procedure. The sperm donor and mother undergoing insemination could be kept unknown to both parties. However it would be unethical not to obtain the consent from the sperm donor regarding what would be done with his sperms. This very

special possibility in a situation of non-availability of any other option would be an alternative to adopting a child. However psychosocial issues and inherent potential paternity disputes need serious considerations before the procedure is embarked upon.

Adoption of a Child

Adopting children is not uncommon, possibly for a variety of reasons. Sub-fertility is the commonest reason for resorting to this phenomenon. However instances of adopting children by at-risk couples have not been reported in the literature. Adopting a child by an at-risk couple may not be different from any other situation of adopting children.

Promoting Safe Marriages

Concept of safe marriage is recognized in Sri Lanka since 1998 by the National Thalassaemia Council as a method for prevention of thalassemia. The main reasons for adopting this strategy were legal sanctions on abortions, social and religious non-acceptance of abortions and lack of facilities for pre-natal genetic diagnosis.

In the specific instance of Thalassaemia prevention, the concept of safe marriage promotes avoiding marriages between two carriers and a safe marriage is defined as "a marriage where at least one of the partners is NOT a thalassaemia carrier". To implement the concept in the society, screening for thalassaemia by full blood count by a haematological analyser is offered to school leavers before they make firm decisions about their marriage partner.

Screening test that is not 100% sensitive could still be safe enough depending on the concept that traditionally, screening of any disease will adopt the most sensitive screening test along with most specific confirmatory test. However the thalassemia-screening test adopted in Sri Lanka; MCV and MCH values done using an automated haematological analyser, is not 100% sensitive as some of the haemoglobin-E beta thalassemia patients can have MCV and/or MCH values within the normal cut-off values. However consideration of the cost constraints of performing the next best option of performing HPLC as the general screening method, the National Thalassemia Council has compromised to accept MCV and MCH values as screening tools.

Sperm Immobilization Jelly

This is only a possible method, a figment of imagination and one that pose a challenge for molecular genetics.

Selection of healthy sperms from the sample of millions of sperms produced in one ejaculate contributes for the success of this potential concept. However artificial insemination may bypass the natural selection process. There is growing interest in natural sperm selection process and selecting healthy sperms for success of fertilization. These innovations have been made possible due to the advancements of the assisted reproductive technologies (ART) and the possibility of intra cytoplasmic injection [24].

Carriers of any genetically inherited disease will have 50% of their sperms with defective genes and 50% of sperms with healthy normal genes. As such, at least technically, developing a mechanism to immobilize or destroy these defective sperms selectively should create a realistic option for prevention of recessively inherited genetic diseases. It is interesting to note that technologies for immobilization of sperms have also been developed to facilitate intra cytoplasmic insertion of sperms.

Alternatively selecting a healthy sperm for intra cytoplasmic sperm injection is also a realistic possibility that has not been given sufficient attention, certainly not as much as the attention given for selection of the ovum.

However detecting unhealthy sperms with defective genes and inactivating them or selecting healthily sperms with normal genes and utilising them has not been sufficiently explored at an experimental level. However, detecting inactive genes within sperms would be a challenging task for molecular scientists.

As the sample of ejaculation is easily accessible researchers have a chance to explore methods of recognising defective genes and go on to develop methods of immobilizing them selectively.

This task may not be easy. Genes in the sperm are inactive and they do not express activity. Therefore only option left would be to use genetic probes to identify the sperms with defective genes. Once the technologies of recognizing defective genes are developed, the second challenge would be to develop methodologies to inactivate them selectively.

If the scientists can overcome these challenges, a selective sperm immobilization jelly would be a reality. We could postulate to think of a day when at risk couples of cystic fibrosis or thalassaemia getting a box of sperm immobilization jelly as their wedding gift or a couple walking to a pharmacy to purchase a vaginal jelly suitable for prevention of a genetic disorder, to which they are vulnerable.

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