REPORT

On prenatal and pre-implantation diagnostic tests
and the question of choice of embryo

The current progress in biomedical and genetic technology makes it possible to apply genetic testing on embryos from very early stages of development, long before birth. Thanks to these tests we are able to identify with accuracy many characteristics of the physiology of the new organism, including information on its genetic make up. It is therefore possible to detect the genetic or developmental causes of many serious diseases. With this knowledge, however, comes a serious moral dilemma: do we have the right to "prevent" the birth of children with such severe diseases by interrupting pregnancy or by not implanting the embryo in the uterus (in the case of *in vitro* fertilisation (IVF)?).

It must be made clear at the outset that prenatal diagnostic tests can also identify treatable conditions, especially at a more advanced stage of development. Modern techniques, for example, allow for microsurgical interventions *in vivo* to repair heart conditions. The above dilemma is irrelevant on these occasions as parents, in addition to the option of interrupting the pregnancy, may also choose to restore the embryo's condition. In ethical terms, this possibility is in no way different from the duty of care for sick children which would, in fact, make the interruption of pregnancy unjustified.

Such treatments, however, are not available – at least not yet – at genome level; that is, we are still incapable of modifying the genetic make up of a new organism in order to eliminate the genetic causes of future illnesses. Gene therapy in embryos currently undergoes clinical trials. It is this incapacity to treat the genetic causes of serious diseases that generates the dilemma of "choice".

In what follows, we will outline the complex parameters of this dilemma to contribute to the preparation of a decision by the Commission. This report will facilitate medical support counselling as well as decision-making by expectant parents, spouses, partners or individuals. It will also illuminate certain issues that fall under the prerogative of the State.

The scientific facts of the overall question are laid out in the first chapter including a brief presentation of the stages of embryonic development and the diagnostic methods. The ethical questions raised by the basic dilemma are discussed in the

second chapter. The third chapter outlines the legal context (in comparative terms as well as the Greek context). In the conclusions a set of proposals are suggested based on the preceding analysis.

1. The biology of embryonic development and the diagnostic methods

Some elements on the stages of embryonic development, useful for the purpose of the present analysis, were discussed in the Commission's report on stem cells.
The time from conception to birth can be divided in three stages.
During the first stage, from the fertilization of the egg to its implantation in the womb, the initial zygote is multiplied by consecutive divisions. In the first three days, the ensuing cells are totally undifferentiated, i.e. they may potentially produce any type of mature cell or membranes and tissues that support embryonic growth (placenta, umbilical cord). These cells are called blastomeres or pluripotential blastocytes.
During the next stage, cellular division continues until the appearance of morphological changes in the zygote which takes the form of a berry (morula): a cavity starts forming in its centre which signals the first cell differentiation. We can then distinguish the generation of peripheral cells (trophoblast) and an "inner cellular mass". The first will form the sustaining material of the new organism (placenta) and the second the organism itself. The trophoblast prepares uterine implantation by producing an enzyme which erodes the uterine wall. The "inner" cells, on the other hand, have already lost their initial pluri-potential and can now be differentiated only into mature cells of the new organism (pluripotential blastocytes). Implantation is completed on the 14th day from conception when cell division has formed the "embryonic disc", the first embryonic development along the axis "head-feet". It must be noted that until the completion of implantation, in the stage of "embryonic disc", the embryo might still be divided into more individuals (monozygotic twins). When the implantation is complete, the embryo is individualized.

The second stage, from implantation to full organogenesis, lasts six weeks. Its termination coincides with the completion of two months from conception. Upon implantation, the trophoblast attaches itself to the endometrium. There, the trophoblast cells stimulate the generation of uterine cells that are entwined with the placenta. The embryo is surrounded by the "chorion" which originates from the

trophoblast and reaches out to attach to maternal tissue. Ultimately, the embryo absorbs the necessary nutrients for its alimentation through blood circulation in the placenta where the embryonic and the maternal blood come in close contact. Following implantation, the morphological development of the embryo begins[1]. Tissues and organs start forming at the fourth week when the first heartbeat appears.
The third stage of embryonic development begins on the ninth week from conception. It involves further differentiation and functional specialization of the vital organs. The embryo is fed, ensures its oxygen intake and excretes the products of metabolism through the placenta. Its arteries which are connected to the placenta *via* the umbilical cord grow thin extensions that end in the maternal blood. From the 18th week on, the mother can feel the embryo's movements. From week 20 onwards, the embryo can survive outside the womb in intensive medical care.

2. Diagnostic methods

During embryonic development it is possible to apply diagnostic methods to collect various information on the condition of the new organism. These methods can be divided into invasive and non-invasive ones.

A. Non-invasive methods

These are methods that do not affect the development of the embryo. They include ultrasonography and maternal blood tests.
By regular sonograms during pregnancy it is possible to identify the position of the embryo, its exact stage of development, multiple gestation, along with certain pathological conditions of embryonic morphology. The accuracy of the test depends not only on technical equipment but also on the physician's personal skill.
Maternal blood tests provide information on protein and hormone contents and severe pathologies of the central nervous system[2]. No risks or injurious effects for the mother or the embryo have been reported with non-invasive methods.

[1] Thanks to hormonal stimuli from the maternal body and special stimuli from the embryonic organism which prevent its rejection as a foreign body.
[2] The «triple screen" (16th-18th week) can identify an excessive concentration of proteins which is an indication of *spina bifida* or a severe cerebral malformation (anencephalia) in the embryo.

B. Invasive methods

Invasive methods identify characteristics of the embryo's genetic make, that is they include genetic tests. Invasive prenatal tests can diagnose chromosomal abnormalities (Down syndrome and other trisomies) as well as monogenic diseases (thalassemia a and b, cystic fibrosis, sex-linked diseases, polycystic kidney disease, etc.). They can also diagnose genetic diseases which are treatable after birth (phenylcetonuria, congenital hypothyroidism, etc.) and thus fall outside the scope of the present discussion. It is estimated that 43/1000 children are born with some form of congenital disease and, of these, 23/1000 with congenital malformations, chromosomal abnormalities or serious monogenic conditions.

In Greece, prenatal tests are applied systematically from the early 1970's, mainly to identify trisomies and thalassemias, leading to effective "prevention" of the latter. Since the late 1980's these tests are also used to detect cystic fibrosis, polycystic kidney disease, Huntington's chorea, etc.

We will distinguish between invasive tests in prenatal diagnosis (PD) *in vivo* and *in vitro* pre-implantation genetic diagnosis (PGD) in the case of IVF.

a) Prenatal diagnosis (PD)

The main methods applied *in vivo* are amniocentesis and chorionic villus sampling. Other invasive methods include embryonic tissue or blood (from the umbilical cord) tests but these are rarely used nowadays. The method of testing embryo cells from the maternal blood circulation is used experimentally for the time being.

Amniocentesis, which is carried out after the 14^{th} week of pregnancy, involves the collection, by puncture, of amniotic fluid from the embryonic sac, which contains embryo cells. Chorionic villus sampling consists of taking samples from the placental tissue and is carried out from the 8^{th} – 10^{th} week of pregnancy.

In both cases, the procedure is monitored ultrasonically. By appropriate processing the cells are separated and their chromosomes inspected microscopically (for chromosomal abnormalities, e.g. trisomies) or subjected to biochemical or molecular/genetic tests (to identify monogenic conditions, e.g. thalassemia or cystic fibrosis). It may take up to 3 weeks for the definitive results to come out (even longer in amniocentesis by which time the development of the embryo has progressed

substantially whereas the results of chorionic villus sampling can be ready in 1-3 days) due to the necessary expansion by cell culture of the relatively small starting sample. The risk of miscarriage from chorionic villus sampling is 2-4% and that of amniocentesis 0,5-1%. The probability of miscarriage, however, is also a function of the skill and experience of the person performing the test.

b) Pre-implantation genetic diagnosis (PGD)

Pre-implantation genetic diagnosis is applied in IVF. This method involves the fertilization of more than one egg *in vitro* in order to increase the chances of pregnancy. For the purpose of this diagnosis, one or two cells are harvested in the first days (usually three) of *in vitro* development (blastomeres/pluripotential blastocytes) from the developing organism which at this time is comprised of 6-10 cells. This material undergoes genetic testing (PCR/polymerase chain reaction or FISH/fluorescence *in situ* hybridisation) to locate chromosomal abnormalities and a number of grave monogenic genetic diseases. To avoid some frequently observed mistakes, the method of CGH/comparative genome hybridisation began to be used recently: it involves the comparison of the chromosomes of the test cell with those of a normal, control cell.

In order to prevent destruction or serious damage to the embryo, this test is preferably performed when the embryo is comprised of at least 8 cells. Besides, in order to ensure certainty of results, the test is replicated in two cells, not just one. Pre-implantation genetic testing can also be applied at a later stage of *in vitro* development (5-6 days following fertilization) in which case the cells are harvested from the already discernible trophoblast. This is not recommended, however, as due to the higher consistency of cells at this stage the risk of damage to the embryo increases[3].

It must be pointed out that although pre-implantation tests can identify the embryo's sex they cannot identify multifactorial genetic features (eye or hair colour, corporal constitution, intellectual skills).

[3] It is also possible to run genetic tests on polar bodies which are formed during the process of maturation of the eggs but here as well the risk of uncertain results is high because chromosomal abnormalities may occur in later stages and thus remain undetected.

Since the early 1990's the methods of pre-implantation genetic diagnosis in Europe (and in Greece) are applied in specialized centres that are able to perform genetic tests in a single cell. The risks involved are connected with the condition of the embryo after the test has been performed. According to certain statistics for Europe (ESHRE), in 97% of the cases the embryos were not damaged by cell harvesting. There is no accurate data about children born following IVF treatment with pathologies, despite testing negative in PGD. To avoid false negative results in PGD, prenatal diagnosis *in vivo* is often performed to confirm the results of pre-implantation testing. A statistical error rate of 3-4% is reported in the latter as revealed by the former.

II. The bioethical context

As mentioned in the introduction, the fact that prenatal diagnostic testing *in vitro* or *in vivo* enables us to identify features of the human organism long before birth raises a fundamental moral dilemma: does the knowing of these features entitles us to select the "appropriate" in our opinion child?

1. Absolute protection of life prior to birth

This question is answered in different ways depending on which position one adopts on the respect and protection of human life and, by extension, on voluntary abortion (or the elimination of embryos *in vitro*).

Of course, the link of "knowledge" to "choice" is not logically indispensable[4]. Indeed, some world outlooks, for instance that of the Christian Orthodox or of the Roman Catholic Church, accept prenatal and pre-implantation diagnosis on condition that it does not lead to abortion or the elimination of embryos. The reason is that, according to these outlooks, human life is equated to a full "person" and enjoys absolute protection from the moment of conception. Therefore, in this case knowledge serves the sole purpose of "preparation" of the expectant parents to respond to the needs of their future child.

[4] To all intents and purposes, the «knowledge" obtained from prenatal testing appears to encourage an affirmative exercise of reproductive freedom. An empirical research (*Modell*, 1988: 39, 40) shows, for instance, that the availability of these tests in populations with an increased incidence of thalassemia (Cyprus) is associated with a high birth increase (precisely due to ensured certainty concerning the health of the expected child).

2. *The argument of "choice"*

The link of "knowledge" to "choice", however, is acceptable both to other Christian confessions (Protestantism) and other religions (Judaism, Islam) as well as to almost all theories of moral philosophy. Basically, these doctrines endorse the protection of human life prior to birth but without equalling it to the protection of the "person". Thus, when weighted against other goods or values, life before birth can be subordinate. Hence, these convictions accept abortion (in various forms) or the elimination of embryos *in vitro*.

By answering the initial question in the affirmative, these doctrines raise the next issue: are we allowed full range of choice or only certain choices, and which ones? Here, the following possibilities present themselves:

a) *Choice based on the health of the expected child ("negative eugenics"):* The first criterion of choice is the need to care for the health of a future human being. By avoiding the birth of seriously ill babies or babies expected to develop serious diseases at a precocious stage of their lives society is said to be proactive ensuring a healthy constitution to young people and at the same time limiting the need of assistance by third parties (family or society).

A counter-argument would be that, in this way, we actually create a mentality of unfavorable discrimination against our fellow human beings who happen to live with a disease from birth instead of promoting a sense of social solidarity which should govern our civilization.

In addition to that, there is the issue of boundaries. For if chromosomal diseases and some monogenic diseases (thalassemia, cystic fibrosis, sex-linked conditions) occur immediately upon birth or, at any rate, shortly after birth, there are serious diseases which are sure to develop but at a relatively older age (at 35-45 years). These conditions (e.g. Huntington's chorea or Alzheimer's disease) are terminal and cause suffering to patients and their kin. The problem is whether our range of choice extends also to these cases or should be excluded in view of the prospect of a normal life until such time as the disease may be manifested.

Finally, what is to be done in case one parent is unwilling to be informed of the results of prenatal diagnosis and the other parent disagrees?

b) *Choice of gender:* As mentioned earlier, thanks to pre-implantation testing, it is possible to detect the embryo's gender at a very early stage. The problem is whether it should be permissible to choose the future child's gender regardless of considerations of health (i.e., the existence of sex-linked conditions). This option is favoured especially as a solution to "family balancing" when there are already more children of the same gender in the family as guarantee for normal family life. The opposing view points out the risk of sexist choices, especially in societies favouring children of a specific gender for reasons related to cultural tradition.

c) *Choice based on considerations of health in favour of another person ("savior sibling"):* A question has emerged in recent years about whether an embryo may be chosen to "serve" as source of treatment for the genetic disease of another. By performing *in vitro* fertilisation of several eggs followed by pre-implantation tests it is possible to prevent the birth of a second child suffering from the same disease. In addition, however, it is possible to choose from the available embryos one which is histologically compatible with a diseased older sibling. This embryo is then implanted so that haemopoietic blastocytes can be obtained from its umbilical cord at birth to use as grafts in order to cure the disease of another child. The opponents of this practice argue that it actually amounts to using a person as a means to an end thereby offending the value of human life. The advocates of this practice, on the contrary, hold that the new child is "credited" with saving a human life, which enhances its human value.

The above discussion does not cover the eventual diagnosis of genetic traits associated with non-pathological phenotypes in the future (hair or eye colour, corporal constitution, even intellectual skills) which would again raise the problem of choice (*positive eugenics*) since – at the moment – there is no such possibility.

III. The legal context

1. International law

Prenatal testing is mainly covered by the laws on abortion and assisted reproduction. On the international level, the Oviedo Convention is the only binding piece of

legislation (upon the states that have ratified it) that contains relevant provisions. Pursuant to these:

a) *In vivo* tests may be performed "*only for health purposes or for scientific research linked to health purposes and subject to appropriate genetic counselling*" (Article 12). The provision refers to a "subject", that is to a person after birth, but logically it should be accepted to apply *mutatis mutandis* in embryos. At any rate, nothing is said about choice of embryo.

b) Pre-implantation diagnosis is permissible as may be inferred from art. 14 which actually does provide for choice of embryo. This may be concluded implicitly from the prohibition of choice of sex except when it is indispensable to avoid a "*serious hereditary sex-related disease*".

Aside from the Oviedo Convention, the issue is not mentioned specifically in any other non-binding special international law instruments on genetics (UNESCO declarations).

2. Comparative law

In most EU states prenatal testing is not regulated by law but in the context of medical ethics rules. The same holds for the US where there is no federal legislation on the issue.

With regard to *in vivo* prenatal testing, we may mention, by way of indication, that France allows it in specially authorized structures, approved by the Reproductive Medicine Authority (Agence de la procréation de l' embryologie et de la génétique humaines). In the UK and Denmark, there is no related legislation. The possibility of interruption of pregnancy due to embryo pathology is available in all the above countries as well as in Italy, Germany, Austria, Sweden, Spain, Portugal and Cyprus (whence the characteristic example of elimination of thalassemia through generalized counselling on prenatal control[5]).

Pre-implantation diagnosis is allowed by law in Denmark, France, Norway and Sweden in contrast to Germany, Austria and Switzerland which forbid it. In Ireland, the prohibition is inferred from the Constitution. Those countries which allow the

[5] The test of future parents for thalassemia is a prerequisite for marriage according to a circular of the Church of Cyprus (but not imposed by law). Thus, if the test results are positive, prenatal control becomes necessary in practice.

method (either by law or according to ethics rules) apply strict requirements especially with regard to licensing the organizations that are authorized to carry out the testing.

A legal review of the issue cannot fail to mention the problem that has emerged in some countries (USA, France, Denmark, etc.) with respect to the right of damages for "wrongful life". The courts were called upon to recognize this right to children born with severe conditions following a mistaken prenatal test. Typically, in France, the *Cour de Cassation* conferred this right to the child[6]. The ruling was met with harsh criticism and led to the adoption of legislation to the contrary effect.

3. Greek law

Prenatal testing in Greece is regulated, on the one hand, by the afore mentioned provisions of the Oviedo Convention[7] and, on the other hand, by the law on abortion.

As to the latter, art. 304 of the Criminal Code allows abortion *inter alia* when "*signs of serious abnormalities in the embryo have been identified by prenatal diagnostic methods which would lead to the birth of a pathological neonate and pregnancy has not advanced more than twenty four weeks*" (case b).

Under this article, the consent of the pregnant woman is required for the abortion. If she is a minor, the consent must be given by one of her parents or her guardian[8].

It must be mentioned, though, that the physician may refuse to perform the abortion in these circumstances for conscientious objections if the continuation of pregnancy does not entail "unavoidable risk against the life of the pregnant woman or risk of serious and lasting damage to her health" (art. 31 of the Code of Medical Ethics/Act 3418/2005).

Finally, there is no law on "wrongful life" in our country.

Conclusions – Proposals

The preceding discussion can lead us to two conclusions:

[6] Affaire Perruche (2000).
[7] And by article 1455 of the Civil Code which essentially reiterates art. 14 of the Convention.
[8] But not against the minor's will according to the correct interpretation of the provision.

a) The portentous moral charge of the fundamental dilemma of "choice" cannot lead to single-minded value judgments. This means, that the dilemma must be answered by each person in the context of their personal autonomy and responsibility. Notwithstanding, a conscious decision greatly depends on thorough prior information: it is the moral and legal duty of the attending physician to provide this information.
b) The State cannot be permitted to interfere with the autonomy of this decision-making or the relationship between the person/s concerned and the attending physician by way of laws or administrative practices. Nevertheless, it has an indisputable role to play in the provision of general and valid information. It is important that citizens be informed of the current possibilities of prenatal testing which must be fully available by public health institutions.
Aside from the issue of information, it is equally important that the legislator be attentive to legal developments in the area and respond in time. Issues settled by case-law in other states ("wrongful life", "saviour sibling") should best be appropriately regulated in advance to avoid legal uncertainty and insecurity about the provision of highly sensitive health services.

Selected References

Aziza - Shuster (E.), Le traitement "in utero": Les libertés individuelles en question, in: *La fabrique du corps humain - Ethique médicale et droits de l' homme*, Actes Sud et Inserm, Arles 1988, p. 85 sqq.

Botkin J.R., Ethical Issues and Practical Problems in Preimplantation Genetic Diagnosis,
J. of Law, Medicine & Ethics 1998, p. 17 sqq.

EGE, *Ethical Aspects of Prenatal Diagnosis*, *Opinion No 6*, 1996.

I. Florentin, Le diagnostic préimplantatoire et le contrôle de la qualité des enfants a naître » in : C. Labrusse – Riou (dir.), *Le droit saisi par la biologie*, L.G.D.J., Paris 1996, p. 109 sqq.

Kanavakis E., Traeger – Synodinos J., Preimplantation Genetic Diagnosis in Clinical

Practice, *J. of Medical Genetics 39, 2002*, p. 6 sqq.

H. Galjaard, *Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention*, UNESCO, Paris 2003.

Gene Therapy Advisory Committee (GTAC), Report on the Potential Use of Gene Therapy in Utero, http://www.doh.gov.uk/genetics/gtac/inutero.htm , 2001.

B. Modell, Ethical and Social Aspects of Fetal Diagnosis of the Hemoglobinopathies: A Practical View, in: D. Loukopoulos (ed.), *Prenatal Diagnosis of Thalassemia and the Hemoglobinopathies*, CRC Press, Boca Raton, Florida 1988, p. 29 sqq.

Nationaler Ethikrat, *Genetic diagnosis before and during pregnancy*, Opinion, Berlin 2003.

Pennings G., Ethics of Sex Selection for Family Balancing. Family Balancing as a Morally Acceptable Application of Sex Selection, *Human Reproduction 1996*, p. 2339 sqq.

Girginoudes P., Papadopoulou D., Agrafiotes A., Papademetriou M., Vosnides G., Loukopoulos D., Presymptomatic diagnosis of polycystic kidney disease with DNA techniques in Greek families, *Iatriki 1991*, p. 275 sqq. (in Greek)

Iapitzakes Ch., Kostaridou S., Iouroukos S., Karampoula A., Loukopoulos D., A case study of juvenile Huntington's chorea with the methodology of molecular genetics, *Iatriki 1991*. (in Greek)

National Bioethics Commission, Report on the "use of stem cells in biomedical research and clinical medicine" (2001), http://www.bioethics.gr .

National Bioethics Commission, Report on the "collection and use of genetic data" (2002), http://www.bioethics.gr .

Kriaris – Katrani (I.), *Genetic technology and fundamental rights. The constitutional protection of genetic data*, Sakkoulas eds., Athens-Thessaloniki, 1999. (in Greek)

Mallios (E.C.), Prenatal testing and the risk of eugenics. Comment in the affaire Perruche (*Cour de Cassation*, 17.11.2000), *ToS* 27, 2001, p. 579 sqq. (in Greek)

Balassopoulou A., Adam G., Loukopoulos D., Prenatal diagnosis of cystic fibrosis. The Greek experience, *Archives of Hellenic Medicine 1988*, p. 472 sqq. (in Greek)

Papadakes M., Karababa F., Boussiou M., Sinopoulou K., Chatzi A., Xenaki M., Antsaklis A. Messogites S., Loukopoulos D., Prenatal diagnosis of thalassaemia and sickle cell syndroms in Greece. I. Prenatal diagnosis through the study of embryo blood, *Iatriki 1991*, p. 353 sqq. (in Greek)

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