Interview with Prof. Jacek Zaremba

Freedom of Choice

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Prof. Jacek Zaremba specializes in genetics, neurogenetics, and clinical genetics. A PAS member, dean of Division Five: Medical Sciences, and a retired professor at the Institute of Psychiatry and Neurology, he focuses on prenatal diagnostics of genetic disorders.

Academia: In Poland, prenatal diagnostic tests remain shrouded in controversy and are widely regarded as a "precursor of abortion."

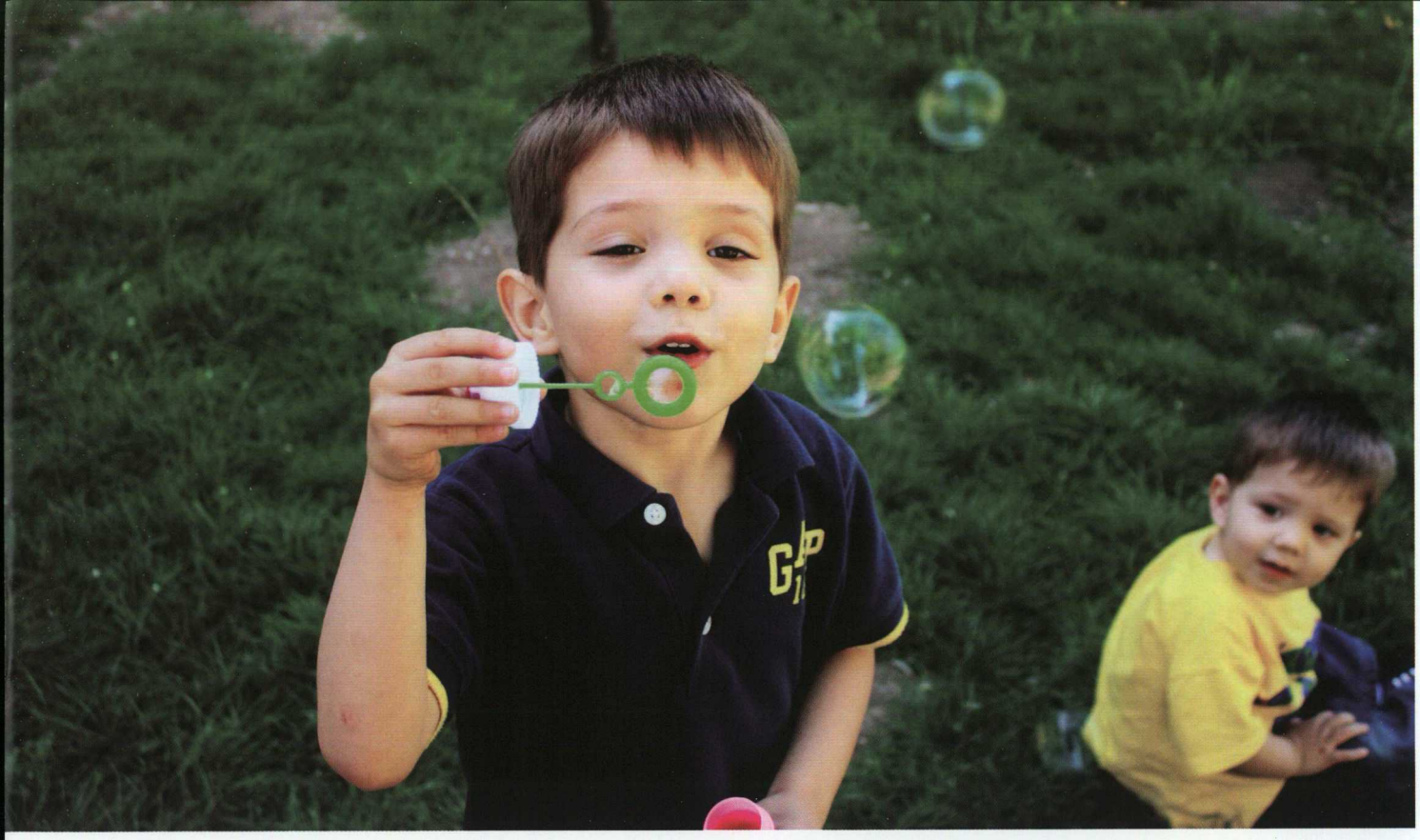
This is in contrast to the rest of the world; in many Western countries, there are even calls to make such tests compulsory for people at high risk of genetic disorders. The matter is looked at from the ethical perspective: should parents risk having babies with serious genetic illnesses, given the high likelihood of suffering faced by the children and their families? As a result, the tests are widely used and social acceptance is high.
Unfortunately, due to social pressures, diagnostic tests are heavily limited in Poland. They have many ideological opponents calling on expectant parents to forgo the tests. However, it is worth noting that doctors refusing to perform tests when high genetic risk is present can suffer serious consequences. There have been situations when doctors either ignored a problem or even promised the parents that their child would be healthy, but the baby was later born with a serious disorder. In the meantime, Poland is increasingly adopting the American model of litigation culture, with growing numbers of lawyers specializing in catching medical errors.
It's important to note that prenatal diagnostics is a highly accountable field. The tests are estimated to be approximately 99.8% reliable (one of the highest ratings in medicine), although mistakes do creep in. For example, a chromosomal aberration may not have been picked up in the tested sample, yet a baby is born with a genetic disorder. This could be because the baby is a case of mosaicism; this means that some of the genetic material is affected, while some is not. We must be extremely careful to provide accurate information to patients.

You have been working in prenatal diagnostics for many years.

The tests date back to the mid-1960s. We were the first institution in Poland to offer them in 1975, at around the same time as the Institute of Mother and Child. We were working at the Institute of Psychiatry and Neurology. Why there? We spent many years studying mental deficiency. We ran a genetics clinic attended by parents of children with an intellectual disability caused by a wide range of factors. We conducted genetic tests to determine the reasons behind these problems. I visited over 100 care homes for mentally deficient children. We studied them while remaining in close contact with their parents; we found out how determined the parents were to be able to have other, healthy children. We were frequently asked about the degree of risk, and how it can be determined. In many cases we were dealing with disorders where we knew what they were, but had no idea how to study their causes. We knew these were genetic conditions, but the key molecular defect remained unknown. It could take as many as ten years for it to be elucidated and for an appropriate prenatal diagnostic test to be developed. We are still faced with limitations; we know more than we used to, but we can't always offer a prenatal diagnostic test, and often can't promise to be able to detect or eliminate a particular genetic disorder during gestation.

You said the tests should be offered to people at high risk; what do you mean by that?

There are many different indications. The most common are cytogenetic, in which there is an increased risk of chromosomal disorders. A classic example is Down syndrome, the most common chromosomal disorder, present in 1 in 600 births. Although having one affected child does not indicate a significantly increased risk of having another, we offer the test to put parents' minds at ease. However, for certain other disorders the



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risk is increased, so having had a child with a chromosomal disorder generally does mean that tests are conducted during future pregnancies.
Another indication is the age of the expectant mother (35 years and over) and any familial structural anomalies which in their balanced state do not cause any problems in the carrier, although they may present a risk that the child's karyotype is imbalanced.
Moreover, all pregnant women are offered non-invasive screening aiming to detect chromosomal anomalies: trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) and Trisomy 13 (Patau syndrome). However, access to screening is limited in Poland, and the costs are usually borne by the parents.

What do the tests involve?

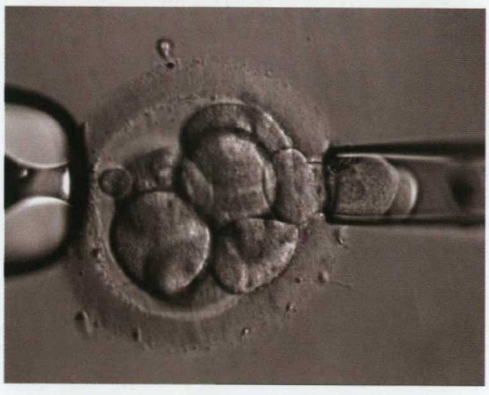
Screening carried out during the first trimester is used to determine a few specific parameters in maternal blood, such as levels of human chorionic gonadotropin (βHCG) and pregnancy-associated plasma protein A (PAPPA). The computer program also considers the expectant mother's age, as well as an important parameter originating from the ultrasound scan: the nuchal transparency measurement, used to assess potential anomalies, carried out between the 11th and 13th weeks of pregnancy. These four factors are analyzed to assess the risk that the fetus is affected by one of the chromosomal anomalies I mentioned above. If the risk is shown to be greater than 1 in 300, the prospective mother is offered an invasive test. The decision remains with the woman; some may regard a risk of 1:300 to be too low to choose to have the test. However, if the risk is greater, I would strongly advise that the tests should be carried out. There is also an option of a test during the second trimester, which involves measuring the levels of alpha-fetoprotein, estrogens and HCG. The first round of screening has the advantage of being carried out earlier, and the tests do not bear any risks. They make it possible to identify women who are at risk despite their young age, and those with no family history of genetic disorders. Unfortunately not everyone is able to afford them. Ultrasound tests are also very important, since they make it possible to determine several different disorders in the fetus; however, the best results are obtained after the 18th week of pregnancy, which doesn't allow the pregnant woman much time to make an informed decision whether she should continue with the pregnancy.

Existing prenatal tests are able to detect a number of different genetic disorders (not just chromosomal anomalies that are relatively common in the general population), involving a specific genetic mutation and/or biochemical defect

The next stage involves invasive diagnostic tests.

There are three different kinds of tests. The first is chorionic villus sampling – a biopsy of the trophoblast carried out around the 12th week of pregnancy. It is an excellent method and the diagnosis is rapid. The second is amniocentesis, during which a sample of amniotic fluid is taken from the amniotic sac. The best time to conduct this test is during the 15th week of pregnancy. Another test, conducted after the 18th week, is cordocentesis or percutaneous umbilical cord sampling. The advantage here is that researchers

are able to quickly grow fetal blood leucocytes and obtain a rapid diagnosis.
Existing prenatal tests are able to detect a number of different disorders (not just chromosomal anomalies that are relatively common in the general population) with genetic conditions, involving a specific genetic mutation and biochemical defect. The problem is that they are offered when we are dealing with a serious genetic disorder, rather as an option to test for all possible defects, since they carry a slight degree of miscarriage. According to our data, the risk doesn't exceed 0.5%, i.e. one in 200 cases. Some people ask why tests should be offered at all, since the risk of the baby having a disorder is 1 in 300 and the risk of miscarriage is 1 in 200. My answer is that while the risks sound similar, half a percent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With pre-implantation genetic diagnosis (PGD), doctors collect one or two cells at the 8-cell stage in embryonic development to determine whether there are any abnormalities

of a sample of a million and half a percent of a sample of a hundred are really quite different. Having a child with a serious handicap is a lifelong decision and may make the parents decide against having more children in the future.

Parents are faced with a difficult choice.

We are always very careful that the decision is taken exclusively by the people directly involved in the situation. We have a strong principle of never revealing our own views. If we are asked what we would do in the situation, we say that we cannot give an answer, and start the conversation again. We are duty-bound to inform the parents what the test results mean, and what Polish regulations say about terminating a pregnancy. We must be certain that we provide all the information the parents need to make their decision, whatever it happens to be. Once they receive the test results, some parents go on to have children with serious disabilities, although they are entitled to choose to terminate the pregnancy instead if they so wish. This is shrouded in serious controversy; however, our experience tells us that the number of abortions carried out following prenatal tests is dropping. We have data demonstrating that before the tests were more widely available, many women terminated their pregnancies for fear of having a disabled child. However, even when the risk is high – for example 25% – in the vast majority of cases the tests results are normal. Look at it this way: 25% is a very high risk when we don't know whether the fetus is healthy. However, when we can test for the disorder, there's a 75% chance that the results will reveal that the fetus is healthy.

There is also pre-implantation genetic diagnosis (PGD), carried out *in vitro*. There's a great deal of controversy about it in Poland, mainly on ideological grounds.

It is difficult for science to argue with people's deep moral convictions. Recently, a well-known professor and Catholic priest made a highly publicized statement about children born as a result of in vitro treatment – utter and horrid nonsense, of course. Prior to that, we were asked to provide input on a bill regulating in vitro and PGD issues, under the commission led by former Justice Minister Gowin. Unfortunately the government instead assigned the task to someone with a very conservative stance, who immediately stated that embryo freezing would never be permissible. It's frightening that people who know nothing about biology, who fundamentally misunderstand its principles, can be in a position to decide whether they allow the use of certain medical procedures. A majority of the people on the commission hold deeply conservative views, including the priest I mentioned earlier. They ended up drafting a proposal we simply cannot agree with. The remaining minority took a different view – and these are people who actually are competent on the matter, since they have a real understanding of assisted human reproduction. We are accused of permitting embryo selection, and yet under natural conditions, the vast majority of embryos affected by serious genetic disorders are eliminated without any intervention. Research demonstrates that most spontaneous miscarriages are the result of chromosomal anomalies. Natural selection is extremely widespread, and that's exactly what we are doing by giving our patients the opportunity to select embryos unaffected by serious genetic disorders; that's what PGD is. The low efficacy of in vitro fertilization – only around 30% – is partly

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due to the fact that without PGD the patients are implanted with embryos including those carrying serious defects, which are very likely to be spontaneously miscarried.

So PGD is an optimal solution?

Yes. Standard prenatal tests detect many genetic disorders, but this can lead to termination for medical reasons. This is frequently a very distressing experience for the mother, both physically and mentally. With PGD, doctors collect one or two cells at the 8-cell stage in embryonic development to determine whether there bear any abnormality. This is especially important in case of serious monogenic disorders. For example, children born with spinal muscular atrophy (SMA) have short, painful lives and usually don't survive beyond two years. Although there are milder forms of the disorder, they are all serious. The risk is 25%; we collect cells and run tests, and find that some of the embryos created in vitro have the disorder while others do not. So we are faced with a question regarding boundaries: does the mother have the right to choose to have the healthy embryo implanted while rejecting those carrying the mutation? For me the answer is clear, and the PAS Committee on Bioethics has also expressed its position in favor. However, there are those who claim that this type of selection is inappropriate and should not be permitted. In spite of these controversies I believe that we should strive to make these tests widely available. This would significantly reduce the need for standard prenatal tests and lessen the stress experienced by a woman on discovering that her fetus is affected. In any case, we conduct standard prenatal tests in order to confirm the PGD results. We have never found any inconsistencies; whenever PGD recognized a genetic disorder, this was later confirmed and the mother has gone on to have a healthy baby. I am very much in favor of this method. I believe that PGD should be available in Poland, in particular in cases when the genetic risk is very high, and financed by the National Health Fund. So far, access to it is extremely limited, and women who wish to have the test are usually forced to travel abroad – if they can afford to, that is.

But surely there should be some boundaries on when the method is acceptable.

The boundaries that shouldn't be crossed mainly stem from the fact that in contrast to prenatal screening, the method isn't used solely for medical indications. Therefore, we need a legal framework to prevent it from being misused. Additionally, I'll repeat that we must leave the final decision to the people directly affected by the situation. If someone makes an informed decision to have a severely disabled child, it is a beautiful choice and many people will regard it as heroic. But we must not demand heroism from all people.

Interview by **Patrycja Dołowy**

Further reading:

Statement on PGD issued by the PAS Committee on Bioethics (in Polish): http://www.bioetyka.pan.pl/images/stories/Pliki/stanowisk%20kb%20nr%20 2-2012.pdf