

PARENTAL ATTITUDE TO PARTICIPATE IN FOLLOW-UP RESEARCH STUDIES OF THEIR CHILDREN'S DEVELOPMENT AFTER DIAGNOSIS OF FETAL ABNORMALITIES IN A TERTIARY CENTER IN ROMANIA

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Abstract

Objective. The main objective of our study was to determine if parents are willing to participate in a follow-up program of their children's development, if diagnosed with congenital abnormalities. The trigger of this research is the gap between the perinatal information and medium/long term implications for the diagnosed cases.

Methods. We performed a double prospective study, based on a questionnaire offered to future parents that addressed in prenatal screening settings, and parents of children attending pediatric clinics for chronic illnesses. We assessed 3 cluster data, related to pregnancy and parental characteristics, and the relation between the parents and the observers.

Results. The vast majority of the antenatal questioned parents were sceptical about taking part in the follow-up program if a major structural anomaly was to be diagnosed. All but one couple with structural anomalies detected prenatally during the study declined the participation. High levels of education, socioeconomic status and difficulties to obtain the pregnancy, were associated with low acceptability. There was a complete absence of correlations between the parents' decision and the severity/outcome of the disease, parity and stated religion variables. The relationship between the observer and parents, the normalcy of scan results and the pediatric setting were consistent with a significantly higher acceptability rate.

Conclusions. Our results suggest that parental decision depends more on the personal views regarding the family and research concept of each couple, than the significance of the anomaly. The results raise the question of bonding and positive perceptions of the research team. Discordant attitude was noted in relation to the timing of the questionnaire. In our settings, most parents consider unacceptable the children's later health investigation for research purposes and worst results were obtained consecutive the prenatal identification of a major anomaly.

Rezumat: Acceptul parental pentru participarea în studii de monitorizare a dezvoltării copiilor diagnosticați antenatal cu anomalii într-un centru terțiar din România

Obiective. Obiectivul principal a urmărit să determine acceptabilitatea cuplurilor de a participa într-un program de monitorizare a dezvoltării copiilor diagnosticați cu anomalii congenitale. Motivul cercetării a fost reprezentat de lipsa de informație pe termen mediu/lung referitor la copiii diagnosticați perinatal cu anomalii.

Metoda. Am realizat un dublu studiu prospectiv, pe baza unor chestionare oferite cuplurilor ale cărori sarcini au fost supuse screening-ului prenatal și părinților care au s-au adresat clinicii de pediatrie pentru afecțiuni cronice ale copiilor. Am evaluat trei clase de date legate de produsul de concepție, caracteristicile cuplului și relația dintre cupluri și personalul medical.

Rezultate. Marea majoritate a părinților chestionați antenatal au fost sceptici cu privire la participarea la studiul de monitorizare în cazul detecției unei anomalii antenatale. Cu o excepție, toate cuplurile la care a fost diagnosticată prenatal o anomalie fetală au declinat participarea. Nivelul educațional și statusul socio-economic ridicat, infertilitatea anterioară obținerii sarcinii au fost asociate cu acceptabilitate redusă. Paritatea, religia declarată și severitatea/prognosticul afecțiunii fetale nu au prezentat semnificație statistică. Relația dintre cadrul

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medical și părinți, normalitatea evaluării fetale și prezentarea în serviciul de pediatrie au fost asociate cu o rată de acceptabilitate crescută.

Concluzii. Rezultatele sugerează faptul că acceptabilitatea prinților de a participa la monitorizarea pe termen lung a copiilor diagnosticați perinatal cu anomalii depinde mai degrabă de impresia personală cu privire la conceptele de familie și cercetare, decât de severitatea anomaliei. Rezultatele aduc în discuție potențialul beneficiu al apropierii dintre personalul medical și cupluri. Atitudinea cuplurilor a fost discordantă, în funcție de perioada interacțiunii cu persoalul medical, față de momentul nașterii. În societatea noastră, cei mai mulți părinți consideră inacceptabilă monitorizarea copiilor lor în scop de cercetare, iar cea mai redusă rată de acceptabilitate a fost constatată în cazurile de anomalii detectate prenatal.

Cuvinte cheie: consimământ parental, diagnostic antenatal, anomalii congenitale, monitorizare.

Introduction

Improvements in ultrasound in recent years have led to an increased number of fetal abnormalities being recognized in the antenatal period and late first trimester anomaly scan became a reality. For many of those conditions, there is good information about the effects up to and soon after birth, but very limited information about the longer term implications for the child. This is a reality, because there is a scarce information obtained from very few long term follow-up (LTFU) studies.

Appropriately conducted studies may lead to important advances in knowledge. There is no published literature from our country concerning the parental attitude towards the LTFU studies. Thus, we attempted to assess the parents' vision about using this tool for gaining information about the LT evolution of conditions diagnosed in utero.

The difficulty in recruiting cases in pediatric long term follow-up (LTFU) trials is notorious. In our country there are additional difficulties, due to the lack of a national electronic database for children diseases.

Being involved in the prenatal diagnostic field, our objective was to assess if parents are willing to participate in a LTFU program of their children's development, if diagnosed with abnormalities.

Methods

A non-anonymous questionnaire was handed to specialists in obstetric ultrasound (working in

screening settings and performing routine ultrasound) and pediatricians, working in clinics and hospitals for sick children. A form was to be offered to future parents and to parents of children attending pediatric clinics for chronic illnesses (having outpatient appointments), in order to be read and accepted. After the consent, the form was completed by the researcher, during an interview in which all solicited explanation were offered to the parents.

This study was designed as a person-centered, individual, open-ended interview, performed by health professionals (doctors involved in the prenatal diagnosis and in child-care).

The parents' opinion on being asked later about their child's health was obtained,

- before and
- after the anomaly scan (both in the first and second trimester), and also,
- at six months and
- one year after the diagnosis of a chronic diseases.

The form was completed in many prenatal settings: PDU - by a PDU observer (who was either the attending physician or an unknown for the couple researcher), and other screening settings, from hospitals in surrounding counties. Parents were informed that the questionnaire would take approximately 15-30 minutes to complete and that involved questions about age, race, education, family background, and their perceptions about medical research. They were also informed that upon

completing the survey, they would receive no gifts/benefits/changing the standard prenatal care in appreciation for their time.

Results

In a prenatal diagnostic setting, before the scan, all couples (483/499) accepted to answer the questionnaire. 93% of them were sceptical about taking part in a follow-up program if a major structural anomaly was to be diagnosed. After the scan, almost all parents of fetuses diagnosed with a major anomaly (92.8%) declined entering a follow-up study.

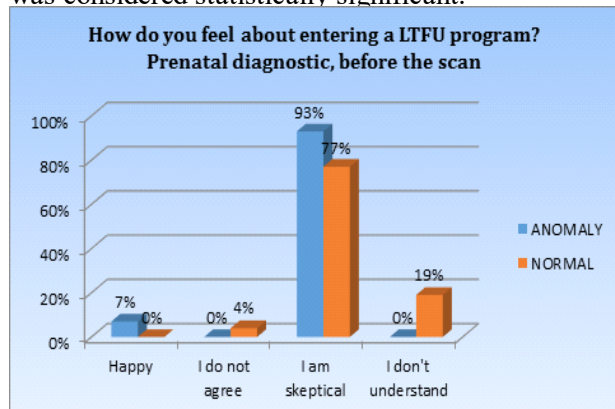
Altogether, we sought to examine 3 constructs governing the decision to provide consent:

- pregnancy characteristics (parity, mode of conception, GA)
- parents' characteristics (median age, education level, socioeconomic status, religion)
- external influences in the decision-making process (relationship with the researcher).

We used basic descriptive statistics and frequencies to describe all variables, comparing

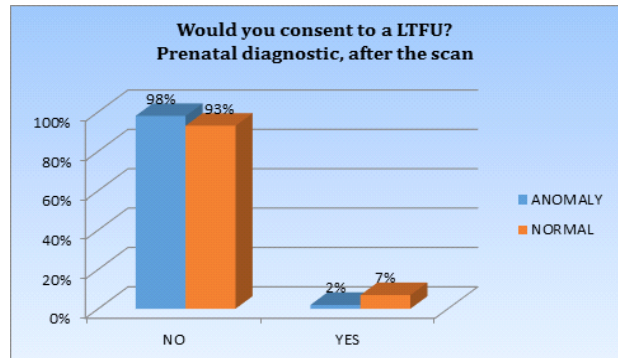
data from parents who consented to enrol their child in the LTFU study with those who declined consent. To determine which factors were significantly associated with the decision to consent we used univariate analyses: Fisher's exact test for categorical variables.

All analyses were conducted with SPSS version 19 (SPSS Inc., Chicago, IL). A p value <0.05 was considered statistically significant.

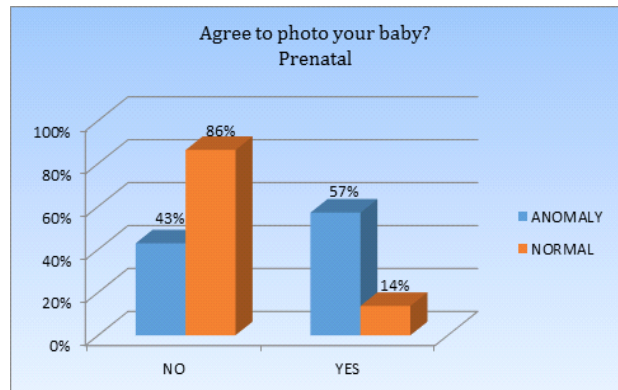


Graphic 1. Representation of the feeling of the parents about entering a LTFU program, before the anomaly scan. Very few couples declared that they are happy about entering a LTFU program for their babies, and the vast majority were sceptical about it.

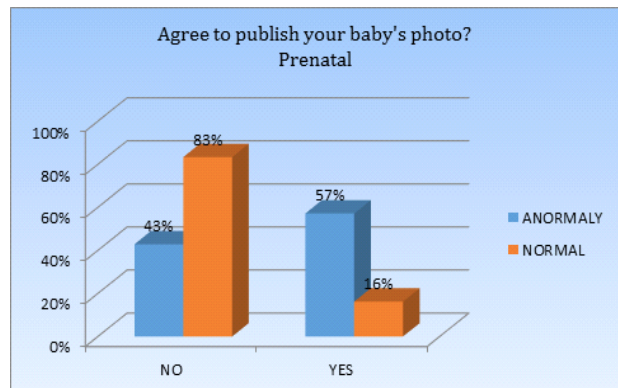
In the paediatric setting, 36% of respondents with long-term health problems accepted the follow-up. More than 90% of parents of disabled children were unhappy to be contacted and asked questions about their children's health and development.



Graphic 2. Representation of the feeling of the parents about entering a LTFU program, after the anomaly scan. Most parents declined.



Graphic 3. Representation of the feeling of the parents about taking photos with their babies. In the prenatal setting, the majority of parents declined.



Graphic 4. Representation of the feeling of the parents about publishing photos with their babies. In the prenatal setting, the majority of parents declined.

The parents' age has a highly significant effect on the feeling about entering a LTFU program (p chi square=1.6784E-10). The parents with age between 25 and 32 have more often the feeling of being sceptical about entering a LTFU program.

Table 1. Mother's education in relation with feelings about entering a LTFU program.

	Primary School	Gymnasium	High School	College	Master	None
Happy	1	0	0	0	0	0
I do not agree	0	0	4	18	0	0
I am sceptical	28	18	92	184	37	12
I don't understand	16	9	42	15	0	6

Table 2. Father's education in relation with feelings about entering a LTFU program.

	Primary School	Gymnasium	High School	College	Master	None
Happy	1	0	0	0	0	0
I do not agree	0	0	4	18	0	0
I am sceptical	27	18	80	208	26	12
I don't understand	17	10	29	27	0	5

The education has a highly significant effect on the feeling about entering a LTFU program (p chi square=2.19401E-10 for Mother and p chi square=1,2975E-6 for Father). The parents with College education have more often the feeling of being sceptical about entering a LTFU program (see tables 1 and 2).

The religion has a significant, but not highly significant effect on the feeling about entering a LTFU program (p chi square=0.01476), the religious parents have more often the feeling of being sceptical about entering a LTFU program.

	Religious	Nonreligious
Happy	1	0
I do not agree	18	4
I am sceptical	241	130
I don't understand	71	17

Table 3. Religious beliefs in relation with feelings about entering a LTFU program.

Discussion

We had rather poor results, although the parents did perceive the long term follow-up program as having low degree of risk, although the operator highlighted the benefits to their child and especially the benefits to other children, and despite the

information about the right to withdraw in any step of the study. This was previously reported (1-6).

Our results confirm (7-9) that having graduated from high school and especially having graduated from college, as well as a higher socioeconomic status were associated with lower likelihood of providing consent. These couples revealed more anxiety about their decision. We may speculate that paradoxically, the higher educated couples displayed significantly lower understanding of study scientific purposes, or that they found it harder to take, on behalf of their child, a decision that could be perceived as humiliating their unborn child. They exhibited more often the perception that by consenting to the study their child will be at danger to a lack of privacy.

Moreover, the study finding that in our setting almost all couples that were confronted with the suspicion/diagnosis of a major anomaly declined entering a LTFU is not surprising, because this is an intense stressful situation, requiring families to deal with many problems, including decision making in terms of their pregnancy management (termination, invasive testing for chromosomal anomalies, prenatal/neonatal surgery, long-term medical treatment). A questionnaire regarding the participation in a LTFU research program was perceived as an added stress for these couples. Many qualified this as an unpleasant

and difficult experience. By contrast, the consenters were more prone to have a lower socioeconomic status and exhibited low decisional uncertainty. It may be the case that these couples had a lower self-esteem and perceive the doctor/the researcher of being a superior professional, able to help the pregnancy survey and their unborn child, so instinctively showed a better compliance.

The operators could not provide interference with standard care, a known factor of influence (10). The LTF program had no potential for enhanced care. There was no availability of a financial stipend, other forms of monetary incentives, and no free examination/medication. There were many couples that asked this simple question: "why should I do it?". The couples were significantly more likely to consent to participate if the researcher was the professional involved in the prenatal care of the respective pregnancy, and this feature rose the hypothesis of bonding or a more positive perceptions of the research team. In our setting on-to-one medicine at parental request is the dominant feature of prenatal care in high socioeconomic status couples. And as expected, the researcher's characteristics or the way he was perceived by the couple could have contributed to the consenting parents' greater understanding of and comfort with the LTFU study and its potential benefit.

The blinding of the process may alter the results, also using financial reward for consenting to LTFU. We did not blind the process.

Digital recording of US examinations is routine in our PDU. The written consent of the pregnant women for using the US images for educational and research purposes is mandatory obtained before the scan. This practice was not altered by the described study. No patient declined the digital recording of the images, video clips and volume datasets in the prenatal case series. In contrast, the consent for taking photographs of the babies was proposed for the first time in our unit. Digital recording (taking photos and videotaping) is ubiquitous in many adult Hospitals. Most health-care institutions do not obtain consent from patients or staff for recording, and use the obtained materials for educational purposes. The digital material is objective, long-lasting and helpful in medical education, health

care research, quality improvement, patient safety, clinical care (11). This have led to its increasing use in health-care settings.

Digital recording has a superiority in knowledge transfer and retention if compared to many other methods of medical education. The same is true for quality assurance purposes (superior to anonymous self-report questionnaires, medical hard copy records, feedback from patients and other forms of retention).

As participants in this process, perspectives of families and patients are important. Still, the acceptability is reported to be high, many patients feel that the method is useful for many healthcare indications and that it would improve the staff performance. In contrast, taking photo of the new born babies/ children to improve medical practice proved to be much more soliciting for researchers, and raises many sensitive ethical questions. We addressed questions in order to assess the parents' opinions about the acceptability, the utility of medical photos, and future uses for research and publishing. The photographic files from children are much more difficult to be achieved, despite the demonstrated advantages in medical practice. Not surprisingly, in our study, we found that most parents perceived the taking photos process of their baby as a threat for privacy.

There were previous reports about the pressure between the desire for reliable research and the need to protect participants from potential moral harm (12,13). Our findings are in agreement to previous studies, that showed a lower compliance for research participation in better educated and high socioeconomic status people (7,8,9). Also our results confirm the parents fear for the direct impact of their child's health if providing consent.

Yet, the results are almost diametric opposed to the published results of Ramsay (2009), to our knowledge the most similar designed study in the literature. We believe that the discordant results may be explained by 4 main differences, present especially in the prenatal setting:

- we used non-anonymous questionnaire, every investigator performed a rather thorough discussion with parents of eligible fetuses, in person.

Also, the form was completed by the investigator, it was not a self-completed questionnaire

- after suspecting a specific fetal anomaly, the questionnaire was applied in real cases, it was not a "scenario" (so assessed an actual situation, not a "mock" one)

- cultural differences

- health system - the subsidizing process is still ongoing, these couples do not have any, or they have a minimal support from state health insurance institutions.

Our findings may be limited because we performed the survey in a certain geographic area (south-west of Romania), and as a consequence, there must be local, cultural, health insurances policy characteristics. However, the strength of our study is that we explored consenting and non-consenting parents whose children were considered either healthy or ill (in the prenatal cohort), and parents' views when their child has different degree of disability. They were all approached for participation in an actual situation, not in a hypothetical clinical trial.

Theoretically, the findings of our study may be used to find new strategies to improve participation in prenatal and postnatal clinical research (13-19). Unfortunately, we found very few modifiable factors that influenced the consent process, the most important being the researcher involved in the recruitment process. If he/she is a trusted professional, well known by the family, it is more likely that he/she will make the couple feel comfortable by consenting for the LTFU study.

Beside this observation, the study highlights the need to empathize more with some couples, and to support them in this process of struggling with the decision (15,17,19). It seems that a tailored approach is needed when discussing research participation with parents, both in a prenatal and in a postnatal setting (12).

Our results confirm, by deduction, that medical research have a potential for mental or emotional side-effects on parents of diseased fetuses/children. Yet, it is difficult to predict and virtually impossible to objective quantify these effects. Parents of children with physical or mental severe problems have been particularly disturbed by being approached to participate in LTFU studies.

We hereby present a representative case in the study. It highlights the changing pattern in parental feelings, function of the moment of the approach in terms of offering the LTFU research studies on their babies. This baby's parents consented to the LTFU study in the prenatal period, before and after the second trimester anomaly scan. In the third trimester, we suspected an extremely complex cortical malformation, with severe ventriculomegaly and periventricular heterotopia and vermian hypoplasia (Figure 1).

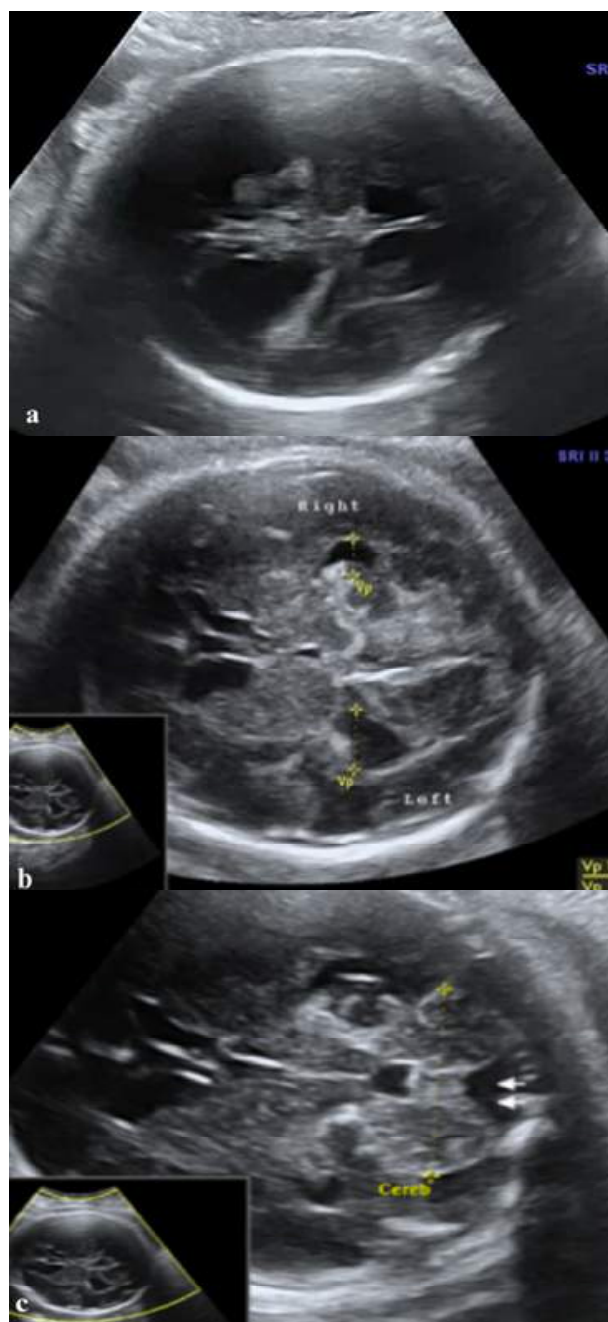


Figure 1. Antepartum images, 32 weeks of amenorrhea. Complex cortical malformation, with severe ventriculomegaly (a) and periventricular heterotopia (b) and vermian hypoplasia (c).



Figure 2. Postpartum images of the new-born. Abnormal ossification of the fontanel and sutures (highlighted – the coronal suture in face view (a) and profile view (b)). This feature led to a non-informative transfontanelar postpartum US examination.

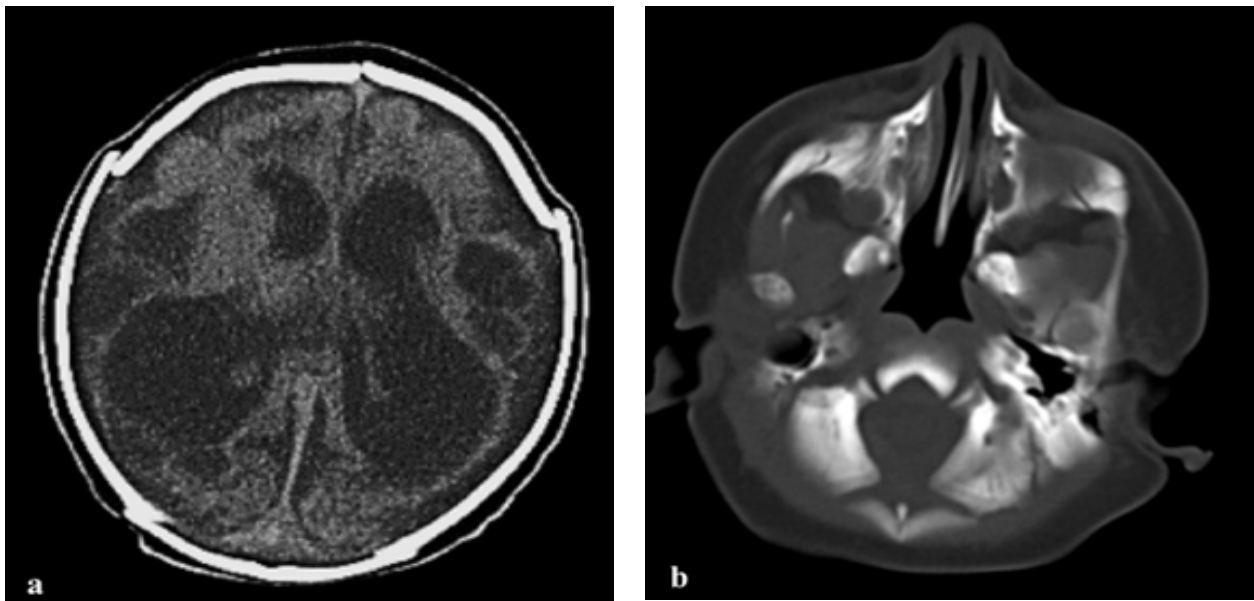


Figure 3. Postpartum computed tomographic images of the new-borne. Cortical hypoplasia.

After counselling, the couple requested and obtained withdrawal. Yet, in the postnatal period, the parents were retrieved in the pediatric neurology recovery program. They accepted the collaboration, so we had access to the neonatal data (that showed a complete ossification of the sutures and fontanel, making the transfontanelor ultrasound non-informative), to the tomographic computed data and to the molecular karyotype, that showed a perfectly normal array-CGH, with a microduplication on chromosome 12, not reported before with clinical significance. Unfortunately, the LTFU showed that the baby (now 3 years old) has severe microcephaly, deep mental handicap, cerebral palsy and spastic quadriplegia.

References

1. E.T. Rosenthal, L.G. Biesecker, B.B. Biesecker, "Parental Attitudes es Toward a Diagnosis in Children With Unidentified Multiple Congenital Anomaly Syndromes", *American Journal of Medical Genetics*, Vol. 103, No. 2, 2001, pg. 106-114
2. P.H. Caldwell, P.N. Butow, J.C. Craig, "Parents' attitudes to children's participation in randomized controlled trials", *Journal of Pediatrics*, Vol. 142, No. 5, 2003, 554-559
3. B. J. Stenson, J.-C. Becher, N. McIntosh, "Neonatal research: the parental perspective", *Archives of Disease in Childhood Fetal Neonatal Ed*, Vol. 89, No. 4, 2004, F321-F324
4. Alan R. Tait, Terri Voepel-Lewis, † Shobha Malviya, "Participation of Children in Clinical Research – Factors that Influence a Parent's Decision to Consent", *Anesthesiology – American Society of Anesthesiologists*, Vol. 99, No. 4, 2003, pg. 819-25



Figure 4. Genetic investigation: conventional karyogram (G- bending) showed a normal karyotype.

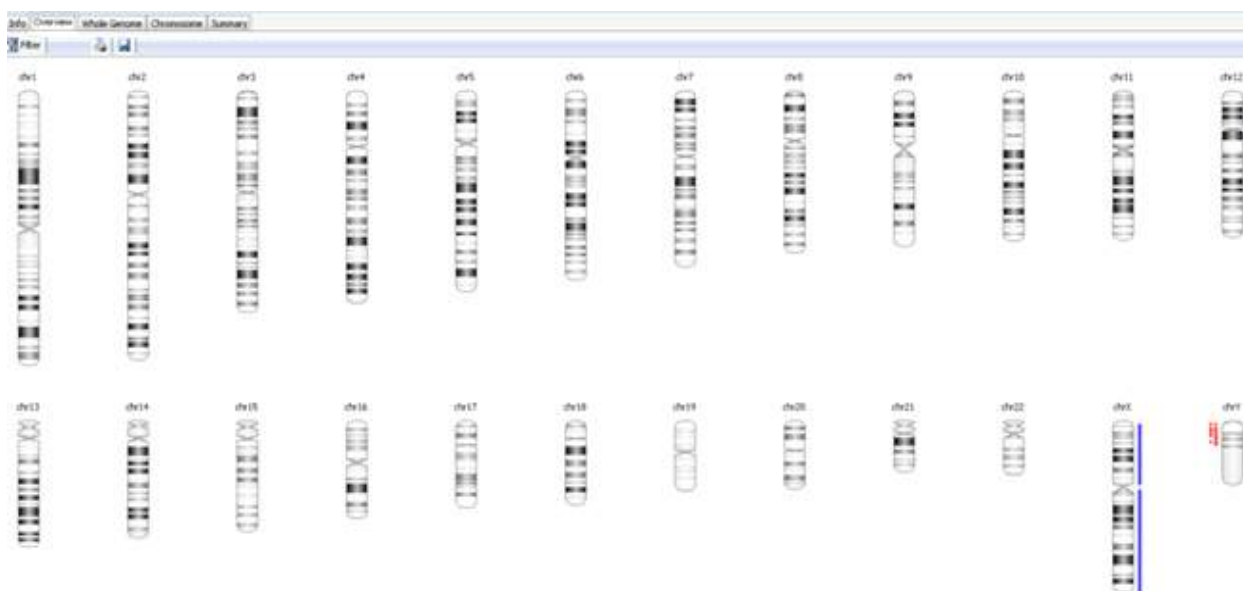


Figure 5. Genetic investigation: array CGH (microarray-based comparative genomic hybridisation) showed a chromosomal 12q11 - q12 microduplication (229 090 bp), with no clinical signification.

5. S. Nicklin, S. A. Spencer, "Recruitment failure in early neonatal research", *Archives of Disease in Childhood Fetal Neonatal Ed*, Vol. 89, No. 3, 2004

6. D. Wendler, T. Jenkins, "Children's and their parents' views on facing research risks for the benefit of others", *Archives of Pediatrics and Adolescent Medicine*, Vol. 162, No. 1, 2008, pg. 9-14

7. Alan R. Tait, Terri Voepel-Lewis, † Shobha Malviya, "Do They Understand? (Part II): Assent of Children Participating in Clinical Anesthesia and Surgery Research", *Anesthesiology – American Society of Anesthesiologists*, Vol. 98, No. 3, 2003, pg. 609-614

8. Alan R. Tait, Terri Voepel-Lewis, † Shobha Malviya, "Do They Understand? (Part I): Parental Consent for Children Participating in Clinical Anesthesia and Surgery

Research", *Anesthesiology – American Society of Anesthesiologists*, Vol. 98, No. 3, 2003, pg. 603-608

9. Alejandro Hoberman, Nader Shaikh, Sonika Bhatnagar, Mary Ann Haralam, Diana H. Kearney, D. Kathleen Colborn, Michelle L. Kienholz, Li Wang, Clareann H. Bunker, Ron Keren, Myra A. Carpenter, Saul P. Greenfield, Hans G. Pohl, Ranjiv Mathews, Marva Moxey-Mims, and Russell W. Chesney, "What Factors Influence Parental Decisions to Participate in Clinical Research: Consenters versus Non-consenters", *Jama Pediatrics*, Vol. 167, No. 6, 2013

10. Justin D. Rothmier, Mary V. Lasley, Gail G. Shapiro, "Factors Influencing Parental Consent in Pediatric Clinical Research", *Pediatrics*, Vol. 111, No. 5, 2003

11. Katherine Taylor, Stephanie VanDenBerg, Ariel le Huquet, Nadeene Blanchard, Christopher S. Parshuram,

- “Parental attitudes to digital recording: A paediatric hospital survey”, *Journal of Paediatrics and Child Health*, Vol. 47, No. 6, 2011, pg. 335-339
12. H.R. Fisher, C. McKeivitt, A. Boaz, “Why do parents enroll their children in research: a narrative synthesis”, *Journal of Medical Ethics*, Vol. 37, No. 9, 2011, pg. 544-551
13. Dove E.S., Avar D., Black L., Knoppers B.M. “Emerging issues in paediatric health research consent forms in Canada: working towards best practices”, *BMC Med Ethics*. 2013 Jan 30;14:5.
14. Lauren Ramsay, David T. Howe, Diana Wellesley, “Parental attitude to participating in long-term follow-up studies of their children’s health after in utero diagnosis of abnormalities”, *Prenatal Diagnosis*, Vol. 29, No. 3, 2009, pg. 207-212
15. H. Chappuy, F. Doz, S. Blanche, J.-C. Gentet, G. Pons, J.-M. Tre’luyer, “Parental consent in paediatric clinical research”, *Archives of Disease in Childhood*, Vol. 91, No. 2, 2006, pg. 112-116
16. Helen M. Sammons, Maria Atkinson, Imti Choonara, Terence Stephenson, “What motivates British parents to consent for research? A questionnaire study”, *BMC Pediatrics*, Vol. 7, No. 12, 2007
17. Irina Korotchikova, Geraldine B. Boylan, Eugene M. Dempsey, Anthony Ryan, “Presence of both parents during consent process in non-therapeutic neonatal research increases positive response”, *Acta Paediatrica*, Vol. 99, No. 10, 2010, pg. 1484-1488
18. Patrina H. Y. Caldwell, Sana Hamilton, Alvin Tan, Jonathan C. Craig, “Strategies for Increasing Recruitment to Randomised Controlled Trials: Systematic Review”, *PLoS Medicine*, Vol. 7, No. 11, 2010
19. R.L. Woodgate, R.A. Yanofsky, “Parents’ experiences in decision making with childhood cancer clinical trials”, *Cancer Nursing*, Vol. 33, No. 1, 2010, pg. 11-18
20. L.M. Slack-Smith, A.W. Read, F.J. Stanley, “Parental attitudes to health of children in child-care centres and options when children are ill”, *Journal of Paediatrics and Child Care*, Vol. 36, No. 6, 2000, pg. 577-580