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Trisomy 13, 18, 21, Triploidy and Turner syndrome: the 5T's. Look at the hands

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Abstract

First trimester spontaneous abortions occur in 15 to 20% of all clinically recognized pregnancies. Chromosomal anomalies are responsible for more than 50% of spontaneous abortions. The majority (90%) of these chromosomal anomalies are numerical, particularly autosomal trisomies (involving chromosomes 13,16, 18, 21, 22), polyploidy and monosomy X. At birth chromosomal anomalies are still an important cause of congenital malformations occurring in 0,55% of newborns (autosomal: 0,40%, sex chromosomal: 0,15%). Autosomal trisomies result from maternal meiotic nondisjunction of gametogenesis and the risk increases with maternal age. Polyploidy (triploidy (3n = 69) or tetraploidy (4n = 92)), results from a contribution of one or more extra haploid chromosome sets at fertilization. Unlike the risk for autosomal trisomies, the risk for polyploidies and for monosomy X (Turner syndrome) does not increase with maternal age. In the prenatal period the ultrasonographic diagnosis of some autosomal trisomies such as trisomy 13 and 18 is feasible based on the frequently seen major malformations while the diagnosis of trisomy 21 often remains challenging due to the absence of major malformations in > 50% of cases. For Turner syndrome (monosomy X), the lethal form will present with cystic hygroma colli and hydrops but the non lethal form is difficult to recognize by ultrasound in the second trimester. The 5 frequently encountered chromosomal anomalies (Trisomy 13, 18, 21, Turner syndrome and Triploidy) referred here as the 5T's have specific hand features which will be discussed.

Key words: Prenatal diagnosis, chromosomal anomalies, trisomy ,triploidy, Turner syndrome, characteristic hands.

Trisomy 13

Trisomy 13 was first described by Thomas Bartholin in 1657 and was cytogenetically discovered by Klaus Patau in 1960 and is therefore referred to as the Patau syndrome. The birth incidence is 1/5000 live births. There is a high fetal loss of 97% for trisomy 13 conceptions and in the postnatal period nearly all trisomies 13 die within 4 months. Trisomy 13 is most commonly caused by a maternal meiotic nondisjunction but a minority of trisomy 13 cases is caused by an unbalanced robertsonian translocation with a high recurrence rate in parental carriership of a 13/14 or 13/15 balanced robertsonian translocation. A postzygotic mosaic trisomy 13 is rather rare (5%) and can have a milder phenotype with a longer survival. Trisomy 13 is typically characterized by a disturbed embryogenesis of the prosencephalon and the midfacies due to a disturbance of ventral induction by the prechordal mesoderm of the primitive forebrain (prosencefalon) (Gilbert-Barness, 2007).

The major phenotypic features are small for gestational age fetuses, with central nervous system (CNS) anomalies, midline facial defects and urogenital malformations.

The main CNS malformation seen in trisomy 13 is holoprosencephaly, but also spina bifida and agenesis of the corpus callosum is possible (Goetzinger

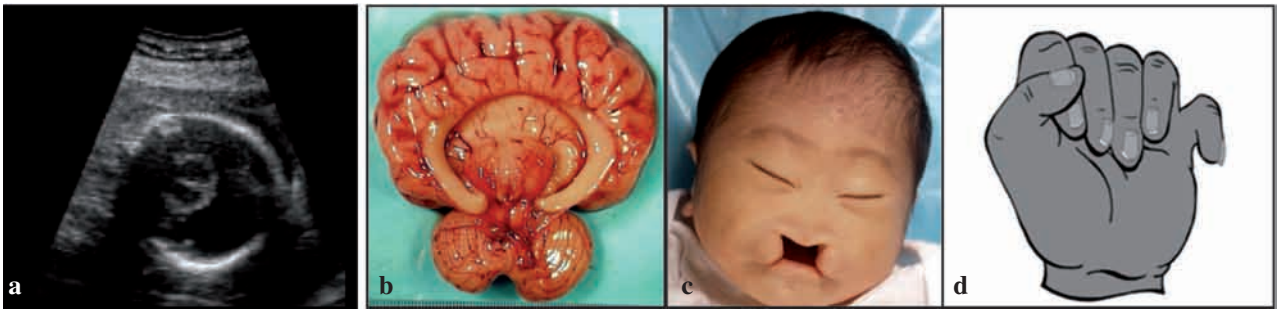

Fig. 1. — a,b) transverse scan in the second trimester showing a monoventricle with fused thalami, typical for alobar holoprosencephaly and the pathology specimen; c) Facial appearance in trisomy 13 with median cleft lip; d) Typical for the hands in trisomy 13 is the postaxial polydactyly (courtesy by Rudi Bagusat (rudi.bagusat@genk.be).

et al., 2008). It is important in these cases to look for other anomalies to give the clue to a cytogenetic abnormality being causative. The alobar type of holoprosencepahly (Fig. 1a, 1b) can be detected by ultrasound (US) from 12 weeks (Papageorghiou *et al.*, 2006; Sepulveda *et al.*, 2004), for semilobar and certainly for lobar holoprosencephaly the US diagnosis is more difficult.

Holoprosencephaly (HPE) can also be caused by other numerical chromosomal abnormalities such as triploidy and trisomy 18.

Aberrant signaling involving the ZIC 2 and TGIF genes are common causes of human HPE, and ZIC 2 is located at chromosome 13q32, while TGIF is located at chromosome 18 p11.2 (El Jaick *et al.*, 2007; Roessler *et al.*, 2009). At present already 13 different autosomal dominant gene loci (including SHH on chromosome 7q36) are known to be involved in the development of holoprosencephaly (Roessler *et al.*, 2009; Solomon *et al.*, 2010).

The facial anomalies typical for trisomy 13 are mainly midline cleft lip / palate (Fig. 1c) and can be severe with arhinia (absent nose), cyclopia (single median eye) and proboscis (an elongated appendage from the head) (Blaas *et al.*, 2002; Lehman *et al.*, 1995; Papp *et al.*, 2006a). Other organ systems that have to be looked at carefully by ultrasound are the heart (80% of trisomy 13 fetuses have a heart malformation such as dextrocardia, atrial or ventricular septal defects), the urogenital system (polycystic kidney 's and genital problems such as clitoral hypertrophy) and the abdominal wall (omphalocoele, in chromosomal aberrations mainly small omphalocoeles with only bowel herniation). Furthermore, an early intrauterine growth delay below the 5the centile has been reported in more than 50% of trisomy 13 fetuses in the second trimester (Watson *et al.*, 2007).

For the hands in trisomy 13 postaxial polydactyly is typical, with small hyperconvex nails (Fig. 1d).

Trisomy 18

Trisomy 18 was first described by John Hilton Edwards in 1960 and is therefore referred to as the Edwards syndrome (Gilbert-Barness, 2007).

It occurs in 1/5000 births but the incidence is higher in the prenatal period with a high percentage of fetal losses. Postnatally 60% of trisomy 18 children die within 2 months and more than 95% within a year. In trisomy 18 mosaicism a longer survival is possible.

The majority of trisomy 18 cases are due to a maternal meiotic nondisjunction with only 5% being caused by a parental balanced reciprocal translocation.

The phenotype typically shows facial dysmorphism with micrognathia, low set abnormal ears, hirsutism (Fig. 2a, 2b, 2d) together with multiple organ system malformations such as spina bifida, omphalocoele, heart defects, clubfeet and radial aplasia (most often unilateral but sporadic cases with bilateral radial aplasia have been reported) (Gilbert-Barness, 2007; Witters *et al.*, 2005; Witters and Fryns, 2008b).

The hands in trisomy 18 fetuses are clenched with camptodactyly with a typical overlapping of the index finger over the middle finger (Fig. 2c).

In the first trimester screening for trisomy 21 and for trisomy 18 by maternal age, fetal nuchal translucency, and biochemistry (free β-hCG and PAPP-A) about 90% of fetuses with trisomy 21 can be identified and about 82% of fetuses with trisomy 18 for a false-positive rate of 3%. The use of a specific risk algorithm for trisomy 18 identifies 93% of affected fetuses at a false-positive rate of 0.2% (Kagan *et al.*, 2008).

In addition fetuses with trisomy 18 show an early intrauterine growth retardation, a relative bradycardia and in 30% of cases an omphalocoele in the first trimester (Bindra *et al.*, 2002).

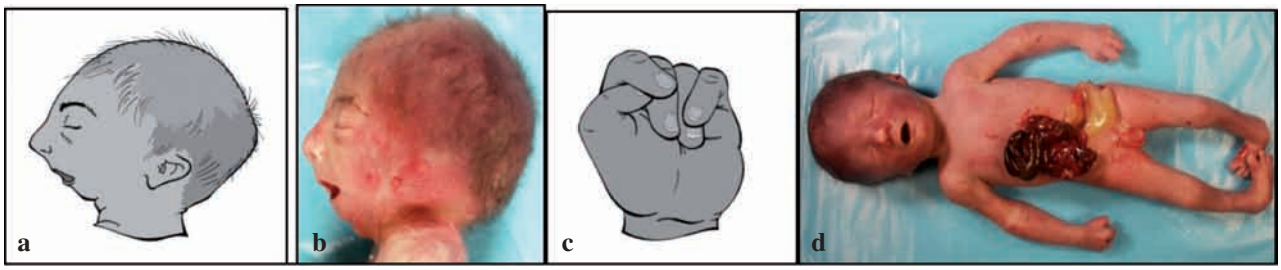

Fig. 2. — a,b) Facial appearance in trisomy 18:micrognathia, low set ears, hirsutism; c) the hands in trisomy 18 with camptodactyly, the index overlapping the third finger and the fifth digit overlapping the fourth (courtesy by Rudi Bagusat); d) trisomy 18 with clenched hands, clubfeet and omphalocoele.

In the second and the third trimester ultrasound we look for the facial dysmorphism typical for trisomy 18 such as micrognathia, abnormal ears and hypotelorism in addition to the typical skull deformation (strawberry skull) (Ettema *et al.*, 2010), symmetrical growth retardation and clenched hands. Again the finding of associated anomalies (facial such as cleft lip, central nervous system such as anencephaly and spina bifida and others such as congenital diaphragmatic hernia, esophageal atresia, omphalocoele, cardiac malformations, clubfeet, and renal malformations) increases the risk for trisomy 18 and justifies karyotyping (Bronsteen *et al.*, 2004a; Brumfield *et al.*, 2000; DeVore, 2000; Oyelese and Vintzileos, 2005; Witters *et al.*, 2001).

Although antenatal trisomy 18 recognition by ultrasound can reach 100% (DeVore, 2000; Oyelese and Vintzileos, 2005), in large-scale studies the antenatal detection rate for trisomy 18 is around 70% (De Vigan *et al.*, 2001; Grandjean *et al.*, 1998). It is important here that the genetic ultrasound is done in a prospective, systematic, targeted fashion by experienced examiners at 19-20 weeks of gestation to detect all cases of trisomy 18 (Oyelese and Vintzileos, 2005). Before 19 weeks the detection of trisomy 18 by a genetic sonogram is lower. In the study by Bronsteen (Bronsteen *et al.*, 2004a), the percentage of fetuses with anomalies at 15-16 weeks, 17 weeks, 18 weeks, 19 weeks and 20 weeks were 67%, 88%, 93%, 100% and 100%, respectively.

The prenatal detection of trisomy 18 remains important, not only because the majority of these children will not survive in the postnatal period due to cardiorespiratory and multiorgan failure , but more importantly because a high rate of unneccessary caesarian sections in this group can be avoided by prenatal diagnosis (Lin *et al.*, 2006).

There has been much debate in the literature regarding the plexus choroideus cyst as a sonomarker for trisomy 18 and the presence of such cysts in low-risk women is an indication for a thorough scan to look for additional malformations with an indication for karyotyping in the presence of any additional finding on ultrasound (Bromley *et al.*, 1996; Bronsteen *et al.*, 2004a; Bronsteen *et al.*, 2004b; Coco and Jeanty, 2004; Gupta *et al.*, 1995).

Trisomy 21

Trisomy 21 was first described in 1866 by John Langdon Down and is also referred to as the Down syndrome. The birth incidence is 1/700 live births.

The risk for offspring with Down syndrome increases exponentially with increasing maternal age. Between mothers younger than 20 years of age and mothers older than 40 years the risk increases from 1/2500 to 1/25.

The majority of trisomy 21 babies (95%) is caused by a maternal non-disjunction during the meiotic division. A minority of trisomy 21 conceptions (4%) are due to a parental balanced robertsonian translocation between chromosomes 13 or 14 and 21 and therefore a karyotype of both parents is indicated after the birth of a Down syndrome baby. Only 1% of trisomy 21 conceptions are caused by a postzygotic mitotic nondisjunction and these mosaic trisomy 21 babies can have a milder phenotype. (Gilbert-Barness, 2007). The phenotype at birth is quite obvious with facial dysmorphism namely a flattened skull, an enlarged tongue, epicanthal folding, brushfield spots (small white spots) in the iris and small low-set ears with a prominent overlapping anti-helix (Fig. 3a). Variable additional malformations/ problems can be present such as hypogonadism, cryptorchidism, cardiac malformations (atrial and ventricular septal defects and atrioventricular canal), duodenal atresia, imperforate anus, and in later life acute myeloid leukemia. The feet can show a sandal gap (wide space between the first and second toe) and syndactyly of the second and third toe.

The hands typically have a simian crease (40%), a distal position of the palmar axial triradius (84%), clinodactyly of the fifth finger (83%) and a hypoplastic second phalanx of the second and the fifth fingers (Fig. 3b, 3c).

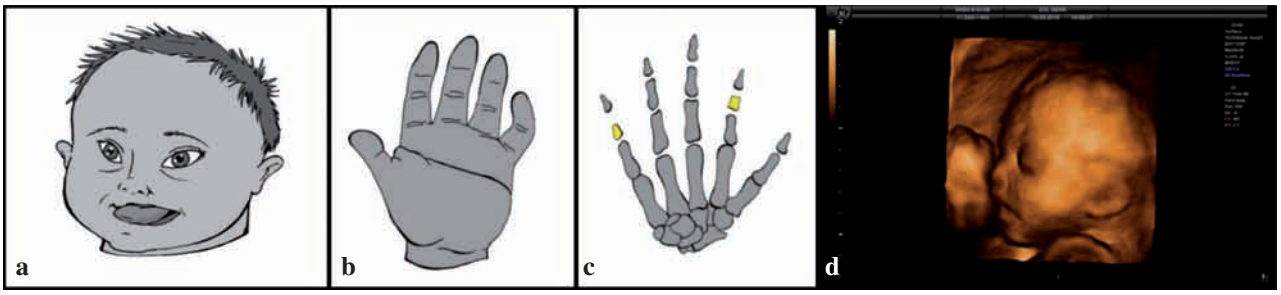

Fig. 3. — a) the facial appearance in trisomy 21: (flat occiput), thick tongue, epicantus, Brushfield spots, small low set ears; b,c) The hands in trisomy 21: simian crease, distal position of the palmar axial triradius, clinodactyly of the fifth finger and hypoplastic second phalanx of the 2th and 5th finger (courtesy by Rudi Bagusat); d) 3D reconstruction of a fetus with trisomy 21 who was diagnosed due to a cardiopathy (AVSD) revealing flat facial profile and low-set ears.

The ultrasound findings for trisomy 21 vary and are much more difficult to detect than those of trisomy 13 and 18.

First trimester combined screening by nuchal translucency thickness and biochemistry (free β-hCG and PAPP-A) can reach a sensitivity of 90% for a specificity of 95% for trisomy 21 in singleton gestations under optimal conditions with trained sonographers performing the nuchal translucency scanning (Avgidou *et al.*, 2005). The presence of the nasal bone will reduce the previously calculated risk with a factor 3 while an absent nasal bone will increase the previous risk with a factor 140 (Cicero *et al.*, 2001; Nicolaides, 2004; Nicolaides, 2005). In expert settings Doppler studies of the ductus venosus (absent or reversed flow during the atrial contraction) and tricuspid valve (tricuspid valve regurgitation) can have an additional value in the first trimester screening for fetal aneuploidy and for cardiac malformations (Nicolaides, 2004; Nicolaides, 2005).

It is useful to look at the first trimester biochemistry (free B-Hcg and PAPP-A), not only regarding the risk for chromosomal abnormalities, but also to understand some other pathological conditions (increased risk for preeclampsia, intrauterine growth retardation,preterm birth, intrauterine death and placental problems) (Table I) (Spencer and Nicolaides, 2002; Yaron *et al.*, 2002).

The second trimester scan can reveal major malformations with a high risk for trisomy 21 mainly 'the double bubble image' linked to duodenal atresia (but also present in a pancreas annulare), often only visible after 24 weeks, a cardiac atrioventricular septal defect (AVSD), an omphalocoele and cerebral mild ventriculomegaly (posterior ventricle = Vp between 10 mm and 15 mm between 18-40 weeks with a 3-4% risk for chromosomal malformations, mainly trisomy 21). All these malformations are indications for karyotyping (Benacerraf, 2008; Langford *et al.*, 2005; Melchiorre *et al.*, 2009; Nyberg and Souter, 2001; Patterson and Costa, 2005; Shipp and Benacerraf, 2002).

Further different sonomarkers have been described increasing the previous risk for trisomy 21: nuchal oedema (measured on a transverse view of the fetal head at the level of the cerebellum > 6 mm) (relative risk (RR) 8-11), echogenic(white) bowel (RR 5-6), short humerus below 5th centile (RR 2,5-6), short femur below 5th centile (RR 2), pyelectasia (measured on a transverse view with antero-posterior measurement > 5 mm) (RR 1-1,5), echogenic intracardiac focus(calcification of a papillary muscle in the left / right ventricle of the heart) (RR 1,4-2), hypoplastic (< 2.5 mm between 15-20 weeks)/absent nasal bone (RR of 80 in the absence of nasal bone) and aberrant right sublavian artery (RR 10) (Benacerraf, 2005; Borenstein *et al.*, 2010; Bromley *et al.*, 2002a; Bromley *et al.*, 2002b; Cicero *et al.*, 2003; Malone *et al.*, 2005; Nyberg *et al.*, 2001; Wapner *et al.*, 2003). The right subclavian artery arises normally as the first vessel from the brachiocephalic artery of the aortic arch. An aberrant right subclavian artery (ARSA) arises as a separate vessel from the aortic isthmus and crosses to the right, behind the trachea. This variant is present in < 1% of the normal population; however, in subjects with Down syndrome, an incidence up to 36% of ARSA has been reported (Chaoui, 2005; Chaoui *et al.*, 2005).

The facial dysmorphism typical for trisomy 21, although more obvious at birth, will be difficult to recognize by ultrasound in a low-risk population of women (Nyberg and Souter, 2001). In high risk women (for example with a known fetal malformation such as an AVSD) facial dysmorphism can be apparent on ultrasound (Fig. 3d). This also accounts for the minor sonomarkers of the hands in trisomy 21 where we mainly look for clinodactyly by ultrasound and the feet where we look for a sandal gap.

Triploidy

Triploidy is caused by an extra set of haploid chromosomes (n = 69) and is present in 2% of conceptuses and accounts for 10% of spontaneous

Table I. — Biochemistry in the first trimester (PAPP-A, free B-Hcg) related to karyotype abnormalities and other bad pregnancy outcomes

Pathology Marker	Trisomy 21	Trisomy 13/18	Triploidy maternal	Triploidy paternal	Other non karyotype related bad pregnancy – outcomes (Preeclampsia, intrauterine growth retardation,preterm birth, intrauterine death) placental problems
Papp-a **B-hCG**	lower higher	lower lower	low low	(lower) high	low (< 0,4 MoM) low (< 0,5 MoM)

miscarriages. It is a frequent cause of first trimester fetal losses (Witters and Fryns, 2008a).

McFadden and Kalousek (McFadden and Kalousek, 1991) divide triploid fetuses into two types. Type I (also called molar triploidy) has the extra haploid set of chromosomes of paternal origin (diandry). Type 2 (also called non-molar triploidy) has the extra haploid set of chromosomes of maternal origin (digyny) (McFadden and Kalousek, 1991).

A paternal triploidy (type 1 according to Kalousek) is caused by dispermy or by the fertilization with diploid sperm, so in these cases the extra haploid chromosomal set is of paternal origin. This results in an hydropic placenta with a partial mole. On ultrasound the placenta will appear thickened with cystic spaces (Fig. 4b). The fetus can be normally grown or mildly growth retarded and can show hydrops (Gassner *et al.*, 2003; Philipp *et al.*, 2004; Salomon *et al.*, 2005).

The recognition of partial molar changes is important since this condition is associated with an increased risk for preeclampsia and for persistent trophoblastic disease (Stefos *et al.*, 2002).

A maternal triploidy(type 2 according to Kalousek) is caused by the fertilization of a diploid ovum and therefore the extra haploid set is of maternal origin. The phenotypic expression shows extreme placental hypoplasia characterized by marked hypermature and fibrotic villi, devoid of molar changes, with asymmetrical intrauterine growth retardation (with a relative macrocephaly), oligohydramnios starting early in the second trimester and a bad fetal condition with fetal demise. Often fetal malformations are present such as holoprosencephaly, agenesis of the corpus callosum, facial dysmorphism with micrognathia and low implanted ears, omphalocoele, cardiac malformations, clubfeet and genital malformations such as cryptorchidism and micropenis (Papp *et al.*, 2006b; Yeo and Vintzileos, 2008).

Again the hands have a typical aspect in maternal triploidy showing syndactyly of the third and the fourth finger (Fig. 4a).

The differences in placentation between paternal and maternal triploidy will also be reflected in the first trimester biochemistry with low PAPP-A en free B-Hcg in maternal triploidy and a high free B-Hcg in paternal triploidy (Table I) (Spencer *et al.*, 2000).

Turner syndrome

The Turner syndrome, described by Henry Turner in 1938, has an incidence of 1/2500 women. The genetic background is variable, with a complete or partial absence of sex chromosomes (the X and / or Y chromosome) (Ranke and Saenger, 2001). The classical karyotype 45, X accounts for only 50% of cases and the remaining cases are either mosaic (combined cellines of 46, XX and 45, X) or karyotypes with an isochromosome of X ((i(Xq) or i(Xp)), and karyotypes with an Y chromosome entirely or partly present (Gilbert-Barness, 2007). Haploinsufficiency of the SHOX gene, located to the PAR1 region of the X and Y chromosome, explains the short stature with mesomelic growth, short fourth metacarpal, madelung deformity (curvature and growth disturbance of the radius), micrognathia and a high arched palate in girls with the Turner syndrome (Clement-Jones *et al.*, 2000; Hjerrild *et al.*, 2008).

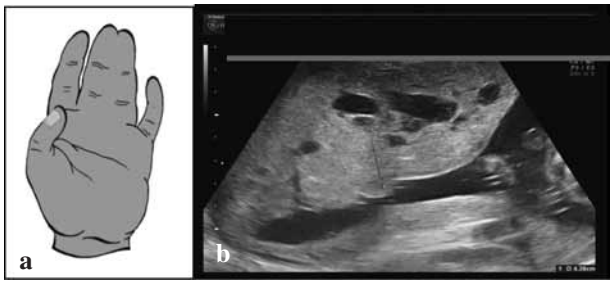

Fig. 4. — a) the hands in maternal triploidy with syndactyly of the third and fourth finger (courtesy by Rudi Bagusat); b) placental aspect in paternal triploidy with thickened cystic appearance.

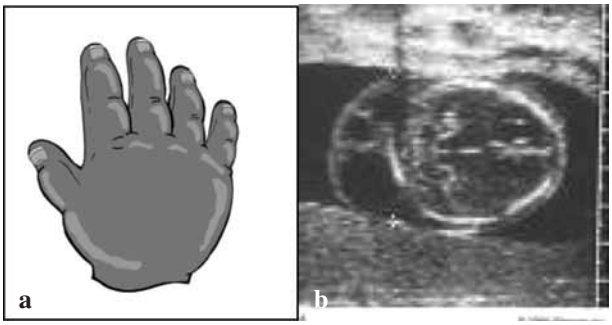

Fig. 5. — a) Turner syndrome hand with lymphedema and short fourth finger (courtesy by Rudi Bagusat); b) Ultrasound of a cystic hygroma in Turner syndrome.

Other known features are gonadal dysgenesis with infertility and premature ovarian failure, endocrine disturbances (hypothyroidism, type 2 diabetes) (Elsheikh *et al.*, 2001; Gravholt, 2005), cardiac malformations (mainly left heart problems such as coarctation aortae) and urogenital problems with multicystic kidney dysplasia and horseshoe kidney (Hjerrild *et al.*, 2008; Papp *et al.*, 2006b).

The typical hand appearance in Turner syndrome (Fig. 5a) is lymphedema of the back of the hand and a shortened fourth finger (short fourth metacarpal). The fetal mortality is as high as 95%.

The lethal phenotype presents with a cystic hygroma colli (Fig. 5b) and hydrops in the first trimester due to a delayed development of the connection between the jugular lymph sacs and the internal jugular vein. Those who survive have regression of the cystic hygroma, resulting in webbing of the neck at that site (Linden *et al.*, 1996; Mostello *et al.*, 1989).

Conclusion

In the prenatal period 5 numerical chromosomal malformations are frequently observed, referred here as the 5 T's: trisomy 13, trisomy 18, trisomy 21, triploidy and the Turner syndrome.

In all these 5 chromosomal abnormalities the hand can be an additional diagnostic tool.

Look at the hands of Figure 6 and do the quiz.

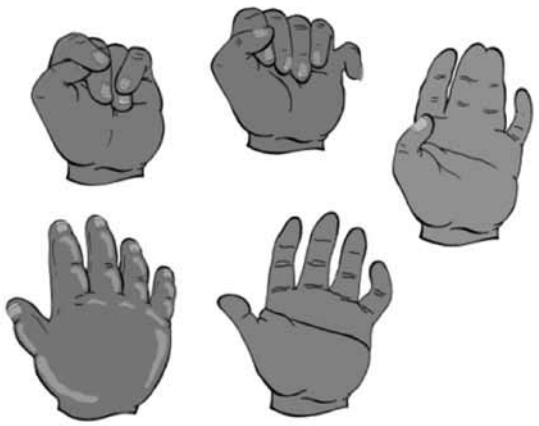

Fig. 6. — Look at the hands. Which hand is typical for trisomy 13, trisomy 18, trisomy 21, maternal triploidy and Turner syndrome? (courtesy by Rudi Bagusat).

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