Congenital Imprinting Diseases: Aetiology, Pre- and Perinatal Manifestations, Diagnosis and Care of Affected Families and Pregnancies

Angeborene Imprinting-Erkrankungen: Ätiologie, prä- und perinatale Manifestationen, Diagnose und klinische Betreuung

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ABSTRACT

Congenital Imprinting Disorders (ImpDis) are caused by abnormal expression of parentally imprinted genes. They are characterized by disturbances of imprinting marks which are a specific type of epigenetic signatures and occur either sporadic or familial. So far, twelve ImpDis have been identified, eight of them manifest prenatally or in the neonate period. With exception of abdominal wall defects, ImpDis are rarely associated with major malformations, but predominant early manifestations are disturbed pre- and/or postnatal growth, muscular hypotonia, neonatal feeding difficulties and metabolic/hormonal dysfunction. With few exceptions prenatal clinical features of ImpDis are unspecific and manifest only in the late second or third trimester. In some ImpDis, behavioural, developmental, and neurological symptoms might emerge, and in single ImpDis there is a higher risk of cancer in childhood.

Prenatal diagnosis plays a crucial role in appropriate pregnancy management and initial care of the newborn, which in turn has positive impact on the life-long outcome of the patient. Furthermore, the diagnosis of ImpDis is relevant for the prevention of pregnancy risks such as preeclampsia and possible reproductive problems in future pregnancies and other family members.

Genetic analysis is not straightforward, and imprinting disturbances may escape both DNA sequencing analysis and (molecular-)cytogenetic diagnostics. After introducing the topic with a case report, this review focuses on the recognition of ImpDis including maternal and family history, exogeneous and genetic risk factors, fetal imaging, and genetic findings as well as interdisciplinary care and treatment approaches in the management and decision making of affected families and pregnancies.

ZUSAMMENFASSUNG

Angeborene Imprinting-Erkrankungen (ImpDis) werden durch eine aberrante Expression elterlich geprägter Gene verursacht. Sie zeichnen sich durch Störungen der Imprinting-Markierungen aus, einer spezifischen Art von epigenetischen Signaturen, und treten entweder sporadisch oder als familiäre Störung auf. Bislang wurden 12 ImpDis identifiziert, davon manifestieren

sich 8 bereits pränatal oder in der perinatalen Periode. Mit Ausnahme von Bauchwanddefekten sind ImpDis selten mit pränatal deutlichen Missbildungen verbunden. Zu den häufigsten frühen Manifestationen zählen pränatale und/oder postnatale Wachstumsstörungen, Muskelhypotonie, neonatale Trinkschwäche und metabolische/hormonelle Dysfunktion. Mit wenigen Ausnahmen sind die pränatalen klinischen Merkmale von ImpDis unspezifisch und zeigen sich erst im späten 2. oder 3. Trimenon. Bei einigen ImpDis können Verhaltens-, Entwicklungs- bzw. neurologische Symptome entstehen, and einzelne ImpDis sind mit einem höheren Risiko verbunden, im Kindheitsalter Krebs zu entwickeln.

Die pränatale Diagnose spielt für ein angemessenes Management der Schwangerschaft und der Erstversorgung des Neugeborenen eine wichtige Rolle, was wiederum positive Auswirkungen auf das lebenslängliche Outcome des Patienten haben kann. Hinzu kommt, dass eine ImpDis-Diagnose für die Vorbeugung von Schwangerschaftsrisiken wie Präeklampsie und mögliche Fertilitätsprobleme bei zukünftigen Schwangerschaften sowie für andere Familienmitglieder relevant ist.

Die genetische Analyse im Hinblick auf ImpDis ist komplex, und Imprinting-Störungen können sowohl der DNA-Sequenzierung als auch der (molekular-)zytogenetischen Diagnostik entgehen. Nach einer Einführung in das Thema anhand eines Fallbeispiels liegt der Schwerpunkt dieses Übersichtsartikels auf der Erkennung von ImpDis und beinhaltet auch die mütterliche und Familienanamnese, exogene und genetische Risikofaktoren, die fetale Bildgebung und die genetischen Befunde sowie die interdisziplinäre Versorgung und Behandlungskonzepte für das Management und die Entscheidungsfindung von betroffenen Familien und bei Schwangerschaften.

Case Report

A 35-year-old gravida I was referred to the Department of Prenatal Medicine in Tübingen because of an abdominal wall defect. At 16 weeks, an exomphalos was detected, containing mainly bowel but also some liver tissue. At 20 and 27 weeks, the kidneys were found to be abnormal. They were larger than expected and echogenic. In addition, the pancreas was prominent, and the placenta was hypertrophic (▶ **Fig. 1**).

Fetal growth and Doppler measurements were within the normal range. An amniocentesis was performed and the results of the cytogenetic, microarray and trio-exome analyses were normal. Due to the suspicion of Beckwith-Wiedemann (BWS) syndrome, cells from uncultured amniotic fluid were analysed for ImpDis and a loss of methylation at the Imprinting Center 1 in 11 p15.5 (IC1) was found, which indicated Beckwith-Wiedemann syndrome (BWS), an Imprinting Disorder. Irrespective from the BWS diagnosis, the fetus died in utero at 31 weeks.

What are Imprinting Disorders?

Imprinting Disorders (ImpDis) are unique among human inherited disease as they are not only caused by genetic alterations, but by aberrant imprinting marks which represent a specific type of epigenetic signatures (for review: [1]). These marks are characteristic for so-called differentially methylated regions (DMRs), i.e. regulative domains in the genome which control the monoallelic and parent-of-origin specific expression of imprinted genes. As a result, either the maternal copy or the paternal copy of an imprinted gene is expressed (▶ **Fig. 2**). It is estimated that about 80 of the more than 20 000 human protein-coding genes are imprinted, whereas the vast majority does not underly this complex regulation.

Genomic imprinting is the basis for a dosage regulatory mechanism for genes involved in growth and development and has an impact on the function of transcription factors. Several of the imprinted genes are involved in prenatal and postnatal growth pathways, accordingly alterations of their balanced expression result in disturbed growth. Interestingly, several paternally expressed and maternally silenced genes enhance (prenatal) growth, whereas maternally expressed factors act as inhibitors (for review: [2, 3]). In addition, altered expression of imprinted genes results in a variety of pre- and postnatal features, among them feeding difficulties and obesity, diabetes, cognitive impairment, tumour predisposition and dysmorphisms (▶ **Table 1**).

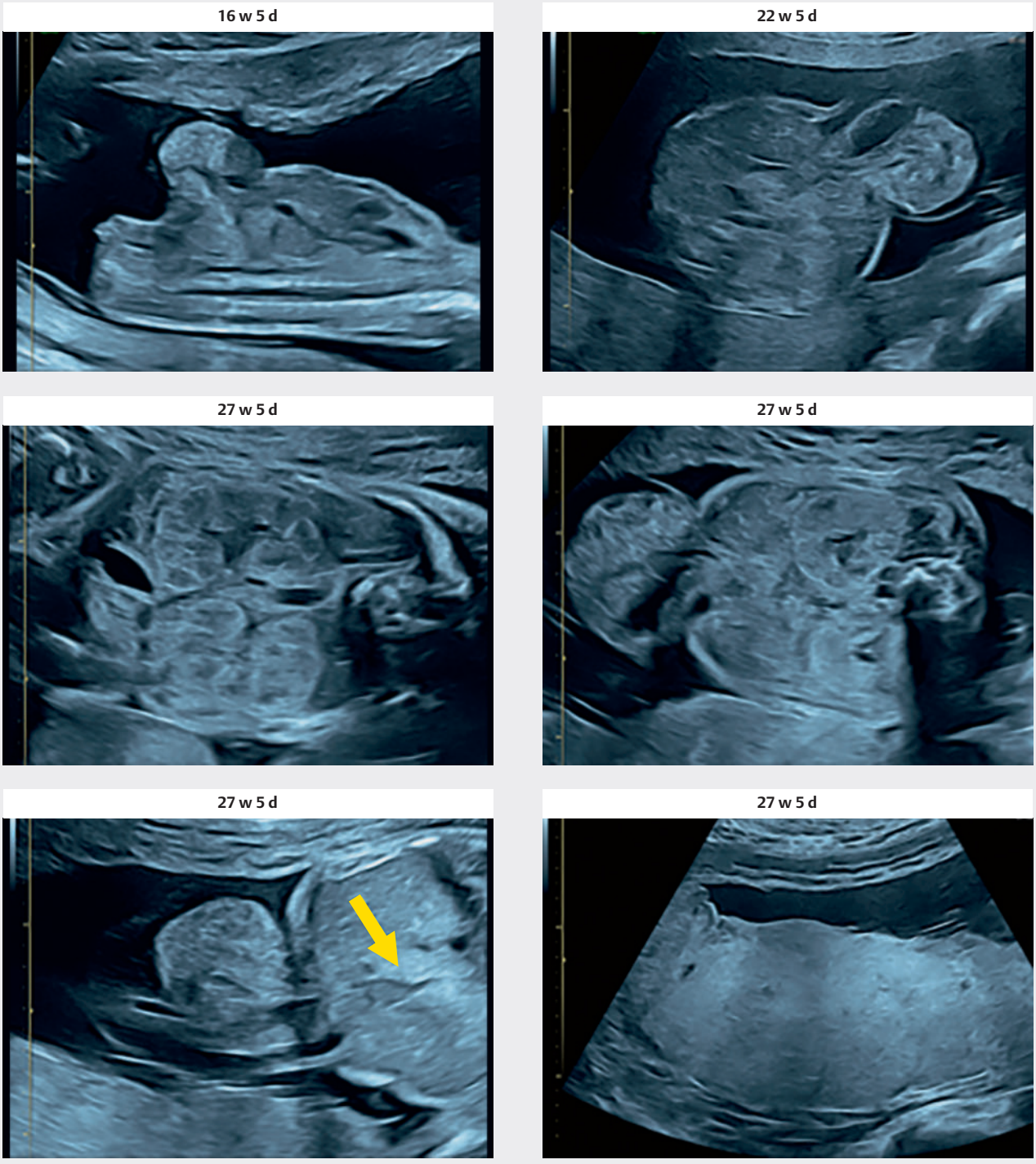
Currently, twelve different ImpDis are known and further have been identified, and the majority of them are caused by the same types of molecular disturbances at different DMRs (▶ **Fig. 2**) but differ in the spectrum of their clinical features (▶ **Table 1**). In fact, several of these features are not disease-specific, and therefore there is a clinical overlap between the different ImpDis making their clinical diagnosis difficult. This observation is reflected by the molecular findings in this group of diseases, revealing a molecular overlap as well (▶ **Fig. 3**) [4].

The prevalence of ImpDis in newborns ranges from 1 : 7000 for PWS to single case descriptions (▶ **Table 1**).

Molecular Disturbances in Imprinting Disorders

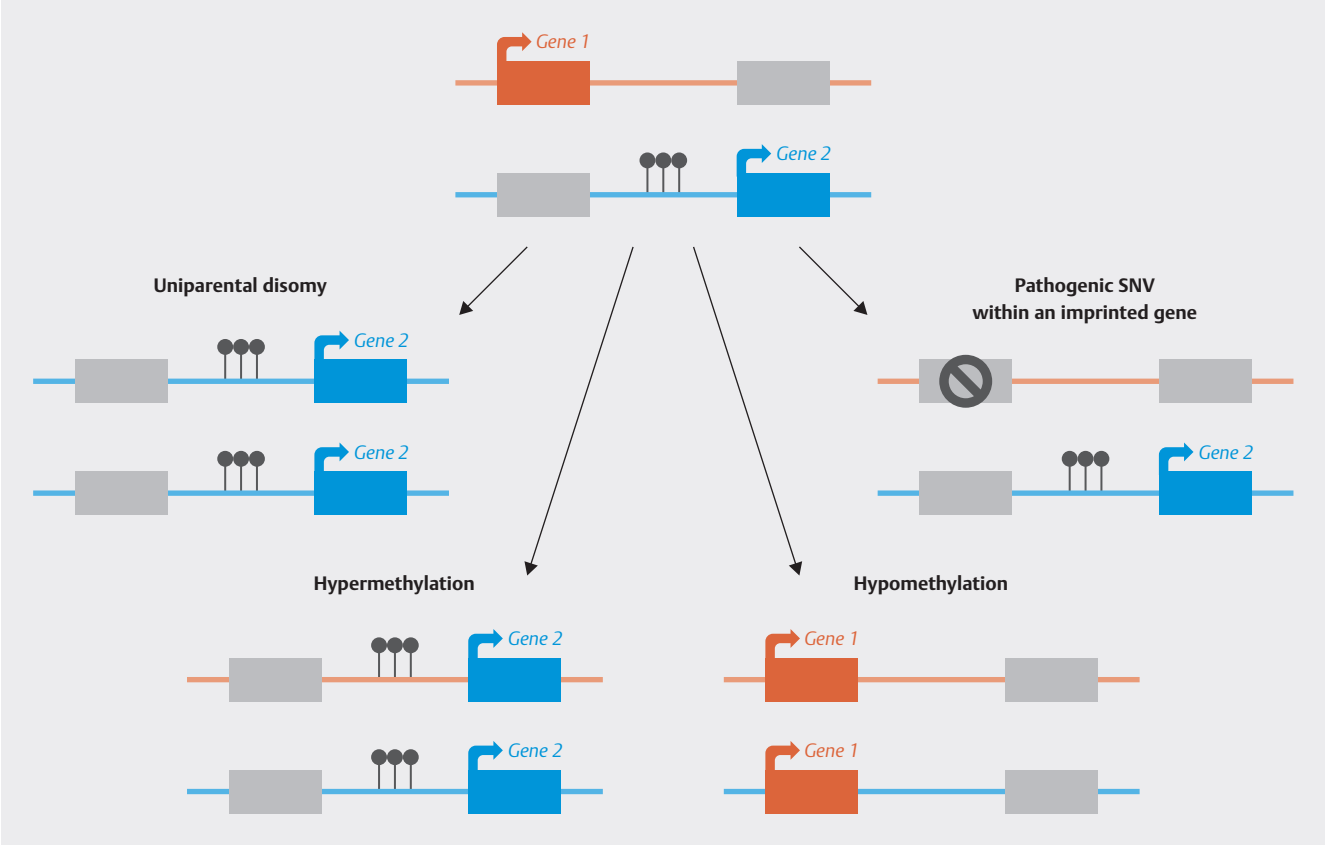
The molecular variants in ImpDis comprise aberrant methylation at DMRs, either hypo- or hypermethylation without any obvious change in the underlying DNA sequence (Imprinting Defects [ImpDef]), as well as genomic changes affecting imprinted chromosomal domains. In some ImpDis, e.g. Angelman syndrome (AS), BWS and Silver–Russell syndrome (SRS), all currently known different types of genomic variants can be observed, whereas others are associated with a single type (for review: [1]).

1. Chromosomal aberrations
   a) Uniparental disomy (UPD) was described firstly described in 1988 [5, 6] and leads to the identification of several ImpDis. UPD is defined as the inheritance of both homologous chromosome of the same parent and is primarily the result of a chromosomal nondisjunction, with trisomic rescue as the most frequent cause [7, 8]. UPD can cause clinical features by altering the parent-of-origin specific expression of an imprinted region.



▶ **Fig. 1** The two upper images demonstrate the exomphalos containing bowel and liver tissue. The images in the middle point out the enlarged and echogenic kidneys. The lower two images highlight the prominent pancreas (left) and the hypertrophic placenta (right) (w: week, d: day).

b) Copy number variations (CNV) of imprinted regions might result in an overdosage (in case of duplication) or a loss of expression (in case of deletion) of imprinted genes. They often do not only affect the imprinted region alone, but dependent on their size they might also have an impact on further genes with an additional impact on the phenotype. A considerable number of CNVs is the result of familial chromosomal rearrangements, such as Robertsonian translocations.



▶ **Fig. 2** Schematic presentation of the four major molecular disturbances affecting imprinting regions, which can be observed in ImpDis. Copy Number Variants (CNVs) are not shown (SNV: single nucleotide variant).

2. Molecular aberrations:
   a) In several rare ImpDis, variants of single nucleotides (SNVs) in imprinted genes are the only variant type which have been reported so far (e.g. Schaaf–Yang syndrome, SYS), but they also account for up to 10 % of cases in the more frequent diseases like AS (*UBE3A*) and BWS (*CDKN1 C)*. SNVs allow clues to the physiological consequences in ImpDis, and might serve as the basis for (future) targeted therapies [9].
   b) ImpDef (also called epimutations) are specific for ImpDis, as they do not alter the DNA sequence itself, but consist of methylation changes of specific CpG islands close to imprinted genes. Currently, two different types of ImpDef are discriminated [10], these are primary ImDef without any obvious molecular cause and secondary ImpDef which are the result of a genomic alteration outside the respective DMR. It has been postulated that exogeneous factors might cause primary ImpDef (e.g. assisted reproduction, endocrine disruptors [11]). The genetic causes for secondary ImpDef comprise a broad range of molecular aberrations (e.g. [12, 13, 14, 15]). Among patients carrying specific ImpDef so-called Multi-locus Imprinting Disturbances (MLID) are observed, in these patients multiple imprinted loci are additionally hypomethylated [16]. Whereas the clinical relevance of MLID for the patients is currently unclear, there is increasing evidence that a relevant cause of MLID are maternal-effect variants, causing reproductive health issues like miscarriages and hydatidiform moles [17].

Another frequent observation of ImpDis is the occurrence of somatic mosaicism of ImpDef and upd(11)pat in BWS, i.e. not all cells and tissues of an individual show the aberration [18]. Accordingly, these variants might escape detection by testing of only one tissue, and false-negative results might be achieved in prenatal as well as in postnatal testing.

Clinical Features Indicating Prenatal Testing for ImpDis

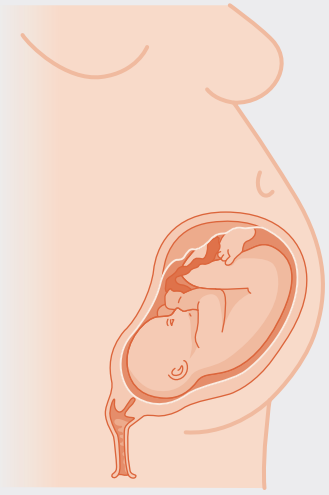
Prenatal clinical manifestations are mostly unspecific and affect fetal or placental growth as well as fetal movement patterns (for review [19]), major defects are uncommon. Some ImpDis may display specific or even pathognomonic features, such as skeletal involvement and single fetal and/or placental dysmorphisms that can be seen by ultrasound as well as by aberrant markers in the maternal blood in the first trimester. The most common prenatal clinical findings in ImpDis are summarised in the following:

▶**Table 1** Overview on the major clinical findings in patients with ImpDis (IUGR = intrauterine growth retardation; PNGR = postnatal growth retardation; 1 = leaned on the review: [1]).

ImpDis	Chromosome	Prevalence1	OMIM#	Prenatal findings	Neonate/early childhood	Postnatal findings
Transient neonatal diabetes mellitus (TNDM)	6q24	1:400 000	601410	IUGR, abdominal wall defects	transient diabetes mellitus, hyperglycaemia without ketoacidosis, macroglossia	Favourable outcome in most cases if the initial symptoms are successfully treated
Silver–Russell syndrome (SRS)	7, 11p15	1:16 000	180860, 618907, 618905, 618908, 616489	IUGR, relative macrocephaly at birth, body asymmetry, prominent forehead	feeding difficulties	PNGR, body asymmetry, (mild) skeletal findings, advanced puberty
Birk–Barel syndrome (BBS)	8q24.3	unknown	612292	less fetal movements	hypotonia	intellectual disability, hypotonia, dysmorphism
Beckwith–Wiedemann syndrome (BWS)	11p15	< 1:10 000	130650	polyhydramnios, placentomegaly, placental mesenchymal dysplasia, macroglossia, exomphalos, lateralized overgrowth	nephroblastomatosis, hyperinsulinism, adrenal cortex cytomegaly, pancreatic adenomatosis	lateralized overgrowth in childhood, normal final size in adulthood; elevated tumour risks: Wilms tumour
Temple syndrome (TS14)	14q32	unknown	616222	IUGR	neonatal hypotonia, feeding difficulties	PNGR, in infancy, truncal obesity, precocious puberty, scoliosis, small feet and hands
Kagami–Ogata syndrome (KOS14)	14q32	unknown	608149	polyhydramnios, placentomegaly, abdominal wall defects, bell-shaped thorax, coat-hanger ribs	respiratory failure just after birth, feeding difficulties	facial gestalt with full cheeks and protruding philtrum, intellectual disability, elevated tumour risk (hepatoblastoma) in childhood
(familial) Central Precocious Puberty (CPPB)	14q32	unknown		no	no	central precocious puberty, obesity, insuline resistency
Prader–Willi syndrome (PWS)	15q11q13	< 1:7000	176270	no	neonatal hypotonia, (severe) feeding difficulties, floppy infant	PNGR, intellectual disability, in childhood: hyperphagia, trunk obesity
Angelman syndrome (AS)	15q11q13	< 1:24 000	105830	no	no	severe intellectual disability, microcephaly, no speech, unmotivated laughing, ataxia, seizures, scoliosis
Central precocious puberty 2 (PPBS)	15q11.2	unknown	615356	no	no	central precocious puberty
Schaaf–Yang syndrome (SHFYNG)	15q11q13	unknown	615547	no	no	delayed psychomotor development, intellectual disability, hypotonia
PHP1 B (iPPSD3)	20q13	< 1:90 000	603233	macrosomia	macrosomia	resistance to PTH (and to TSH in some cases)

* The reported prevalence for BWS might be underestimated due to undiagnosed mosaic cases and individuals with milder phenotypes.

Preeclampsia:
BWS



Intrauterine aberrant growth:
Growth restriction: SRS, TS14, TNDM, PPHP, PHP1A, MBCS
Overgrowth/macrosomia: BWS, KOS14, (PHP1B)

Polyhydramnios:
BWS, KOS14

Abdominal wall defects, exomphalos:
TNDM, BWS, KOS14

Placenta:
Placental mesenchymal dysplasia: BWS
Placentomegaly: KOS14, BWS
(some BWS show placentomegaly but not mesenchymal dysplasia)

a

Postnatal features of imprinting disorders

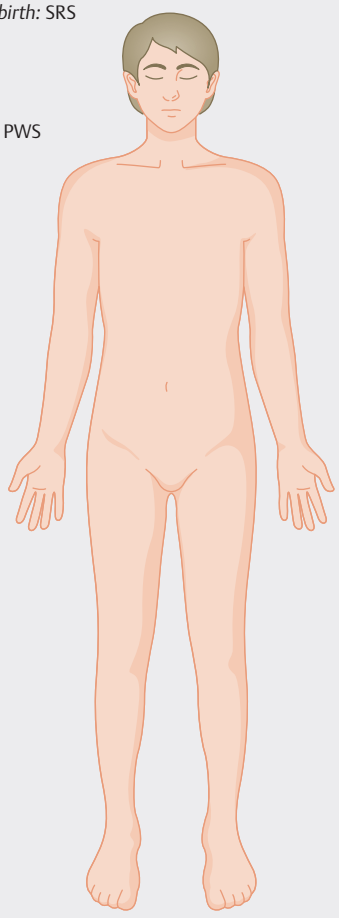
Head circumference:
Relative macrocephaly at birth: SRS
Microcephaly: AS

Facial gestalt/dysmorphisms:
TNDM, BBS, SRS, (TS14), KOS14, PWS
Macroglossia: BWS, KOS14

Developmental delay:
SRS, TS14, KOS14, PWS, AS, SYS, (PHP1A), MBCS

Growth/lateralised growth:
(Intrauterine) restriction: SRS, TS14, PWS, MBCS
Overgrowth: BWS, KOS14

Puberty:
Advanced: SRS, TS14, CPPB, CPPBS
Delayed: PWS



Intellectual disability
BBS, KOS14, PWS, AS, SYS

Neurological symptoms
Ataxia, seizures: AS

Endocrinology
TSHr: PHP
PTHr (progressive): PHP
Hypersensitivity to PTH: MBCS

Cardiac lesions
(BWS), (SRS)

(Insulin) metabolism
TNDM, SRS, BWS, TS14, CPPB, PHP1A

Abdominal wall defects
TNDM, BWS, KOS14

Tumor predisposition
BWS, KOS14

Hypotonia
SRS, BBS, TS14, PWS, SYS

Feeding/nutrition
Feeding difficulties/dystrophy:
SRS, TS14, KOS14, PWS, MBCS
(Trunk) obesity/hyperphagia:
(SRS), TS14, PWS, CPPB, PHP1A

Skeletal findings
Bell shaped thorax/coathanger ribs: KOS14
Scoliosis: TS14, AS
Small hands/feet: TS14, PWS
Heterotopic ossification: PHP1A, PPHP, POH
Advanced bone age: PHP1A
Brachydactyly: PHP1A, PPHP

b

▶ **Fig. 3** The clinical key prenatal (**a**) and postnatal (**b**) features of ImpDis, illustrating the clinical overlap.

Aberrant prenatal growth, manifesting usually in the late second or third trimester is the most obvious prenatal manifestation in ImpDis. Fetal growth restriction is seen in SRS and Temple syndrome (TS14). Sonographic findings are mostly helpful to discriminate between non-genetic risk factors or chromosomal and monogenic diseases. Besides maternal determinants, exogenous causes and placental disorders as well as chromosomal aberrations (including confined placental mosaicism) are commonly associated with fetal growth restriction. Fetuses with structural malformations, with or without chromosomal or genetic abnormalities have an increased risk for fetal growth restriction.

Fetal overgrowth is seen in BWS and Kagami–Ogata syndrome (KOS14). Prenatal overgrowth is also but rarely associated with chromosomal disorders (Pallister–Kilian syndrome [tetrasomy 12 p]) and may be diagnosed in some rare monogenetic disorders (e.g. Simpson–Golabi–Behmel syndrome, Sotos syndrome, Weaver syndrome, Perlman syndrome, PTEN hamartoma tumour syndrome, *PIK3CA*-related segmental overgrowth, Klippel–Trenaunay syndrome and Parkes–Weber syndrome). However, after exclusion of a maternal diabetes, BWS remains the most important syndromic association. In summary, ImpDis should be taken into account in all fetuses with growth disturbances.

Exomphalos can be isolated but is more frequently associated with syndromic conditions such as the common trisomies 13, 18, and 21 and several rare conditions that can be identified by additional specific ultrasound findings (i.e. Pentalogy of Cantrell or Cloacal exstrophy [OEIS] syndrome, Charge syndrome, Meckel–Gruber syndrome). However, after exclusion of chromosomal abnormality, BWS is the most prevalent syndromic association. An exomphalos can also occur in PWS. Therefore, we suggest that in the absence of other features, multilocus methylation testing targeting all clinically relevant imprinted loci might be considered as a first tier investigation in all cases with exomphalos.

Polyhydramnios is another relevant prenatal feature in BWS and KOS14, but it has not yet been systematically evaluated for other genetic diseases.

Despite these prenatal ultrasound findings, clinical signs of ImpDis are often detectable only antenatally. In fact, several ImpDis are associated with clinical symptoms in the neonatal period that require an immediate and intensive neonatal care. For example, patients with PWS usually show hardly any prenatal abnormalities, however reduced fetal movements and breech presentation (severe fetal muscular hypotony), as well as delayed delivery possibly due to oxytocin deficiency [20] may occur.

Reproductive Health Issues, Recurrent Miscarriages and Hydatidiform Mole

In women or families with recurrent miscarriages of unclear aetiology, especially with evidence of hydatidiform moles in the maternal or family history, testing for multiple imprinted loci should be considered [16] to identify MLID. In case MLID is confirmed in the fetus, genetic counselling has to be offered, and diagnostics for maternal effect mutations in the woman might be initiated. The occurrence of MLID can be associated with pathogenic maternal effect variants [21]. Maternal effect variants affect genes which encode factors involved in oocyte maturation and metabolism of the early embryo prior to the activation of the fetal genome, including imprinting maintenance [14]. Women carrying these variants are at increased risk for reproductive health issues such as recurrent miscarriage, hydatidiform mole and preeclampsia. The phenotypes of MLID in a family can range from early abortions to live-born children with different ImpDis (for review: [17]). In fact, it is difficult to estimate the outcome of pregnancies in these women as it cannot be predicted which imprinted loci might be disturbed.

Specific Risk Factors for ImpDis and Their Implications

As fetal imaging and prenatal clinical manifestations of ImpDis usually only provide clues without being specific, a thorough documentation of the medical history can be the key to diagnosis. In fact, several risk factors for birth of child with an ImpDis have already been identified (Box 1).

BOX 1

When should testing for Imprinting Disorders be considered?

- Mode of conception: artificial mode of conception
- History:
  - Parent or previous child with imprinting disorder or positive family history
  - Habitual abortion and multiple hydatidiform moles in the history of the pregnant woman, her sister or in her female paternal relatives (i.e. MLID)
- Chromosomal anomalies:
  - Familial structural chromosomal variants of chromosome 6, 7, 11, 14, 15, 16* or 20 in one of the parents
  - Confined placenta mosaicism involving chromosome 6, 7, 11, 14, 15, 16* or 20
  - Small supernumerary derivate chromosome at prenatal karyotyping that could originate from chromosome 6, 7, 11, 14, 15, 16* or 20
- Characteristic ultrasound findings:
  - Growth anomalies of the fetus (macrosomia, IUGR) and/or the placenta
  - Organomegaly
  - Macroglossia
  - Abdominal wall defects
  - Polyhydramnios

* Whereas the other chromosomes are associated with ImpDis, for chromosome 16 is it currently in discussion whether a specific ImpDis exists [22].

Positive family history for ImpDis

ImpDis usually occur sporadically. However, exceptions exist, and it is important to recognize that ImpDis do not necessarily follow Mendelian rules of inheritance. Therefore, recurrence risks and clinical features might be different depending on the parental

origin. Specific situations with a significant recurrence risk include a parent with ImpDis (i.e. SRS, BWS), and a previous child with ImpDis or an ImpDis in the family. As recurrence risk may vary (virtually zero to 50 %) according to the specific molecular basis of the ImpDis, a thorough genetic evaluation is necessary to provide individually tailored prenatal diagnostics and pregnancy management.

Recurrent miscarriages as well as hydatidiform moles of unknown cause in the mother's history, her sisters or one or more of her female paternal relatives might be associated to a maternal effect variant and MLID, with significant recurrence risk.

Prenatal chromosomal findings or familial structural chromosomal variants involving imprinted chromosomal regions

UPD as well as CNVs (deletions/duplications) of imprinted chromosomal regions bear a significant risk for ImpDis. UPDs are mainly the result of trisomic rescue (for review: [23]). Advanced maternal age and *de novo* or familial structural chromosomal aberrations are risk factors for chromosomal nondisjunction and aneuploid conception. Additionally, certain cytogenetic findings associated with an increased likelihood of UPD are mosaic trisomies in prenatal diagnosis, including confined placental mosaicism (CPM), as well as the detection of a supernumerary marker chromosome [24].

CNVs most likely occur *de novo* without or with minimal risk of recurrence in case of parental germline mosaicism. However, in few instances familial CNVs of imprinted regions with a 50 % risk of recurrence in the offspring of an affected parent have been described. It should be noted that familial CNVs involving both paternally and maternally imprinted genes may be associated with different phenotypes within the same family, depending on whether the aberration was passed from the father or the mother to the child.

Mode of conception

Several studies have shown an increased rate (up to a 5–10-fold) of ImpDis (BWS, AS, PWS, and SRS) in children born after assisted reproductive technologies (ART) [25, 26, 27, 28, 29, 30]. As the overall risk is low, ART does not warrant diagnostics approaches, but the mode of conception should be considered when ImpDis associated findings are detected on fetal ultrasound (▶ **Table 1**).

Based on these observations, we suggest three steps towards the diagnosis of an imprinting disorder:

- Step 1: fetal ultrasound, indicating fetal anomalies consistent with ImpDis.
- Step 2: genetic counselling and invasive testing including karyotyping, microarray and/or trio exome analysis (dependent on the national guidelines and health systems).
- Step 3: in case of a normal genetic testing result from step 2 molecular testing for ImpDis.

However, as several ImpDis are not associated with characteristic prenatal features, prenatal testing or ImpDis should be considered in families with a history predisposing for such a disease (Box 1).

Genetic Methods in Prenatal ImpDis Diagnostics and Their Limitations

Molecular genetic testing in ImpDis is challenging because of their molecular and clinical heterogeneity and overlap.

A broad set of diagnostic methods for ImpDis testing is currently available, targeting single loci, a bundle of loci or the whole genome. Though whole genome analysis harbours the potential to cover all molecular variants, its application should be considered carefully as genetic testing should be adequate and incidental results should be avoided [31], particularly in prenatal testing.

It has generally been consented that first step diagnostics of ImpDis should target loci and variant types which are associated with ImpDis. In ImpDis for which only SNVs in single genes have been reported to be altered (e.g. SYS), diagnostic testing might be restricted to sequencing analysis of the respective gene. Methylation-specific assays should be used as first-line tests in disorders in which UPDs and ImpDef are the major defects (e.g. BWS, SRS). In these ImpDis, stepwise diagnostic testing might be applicable [32, 33, 34].

In any case, as there is a broad spectrum of methylation-specific tests, the lab must be aware of their methodological limitations. It is recommended that a lab implements and runs tests which covers all frequent pathogenic variants known for the specific disorder. An example is PWS and AS testing, where more than 70 % of patients are caused by deletions in 15 q11.3. Despite this high frequency, it is not sufficient to conduct Fluorescence-*in situ*-hybridisation, but methylation-specific assays have to be applied as they allow the detection of deletions, UPD and ImpDef in parallel and are thereby faster and provide a much higher detection rate.

It must be noted, that ImpDef and some UPDs tend to occur as mosaicism in different prenatal and postnatal tissues. Therefore, they can escape detection, and this limitation has to be described explicitly in negative prenatal testing reports [35]. The decision about the invasive prenatal testing procedure has also to consider that not all imprinting marks are stably established in the early pregnancy, accordingly analysis of chorionic villous samples might provide false results. Finally, cell culturing also has an impact on methylation patterns, therefore native prenatal samples should be tested for imprinting patterns.

Conclusion

Though ImpDis are currently rarely diagnosed, they considerably contribute to the genetic causes of aberrant ultrasound findings. As the elucidation of these causes serves as basis for the management of pregnancy and birth, it is relevant to be aware of the genomic alterations associated with ImpDis, and to include their testing in the prenatal diagnostic workflow. The indications listed in Box 1 might help to contribute to the decision-making process in which situations ImpDis testing should be applied prenatally.

Conflict of Interest

The authors declare that they have no conflict of interest.

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