ACPA & Cardiopathies Congénitales en prénatal

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Epidémiologie :

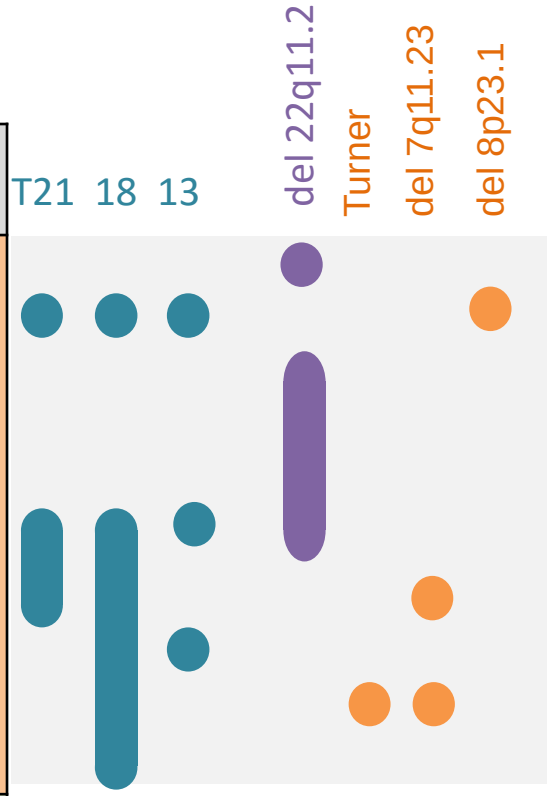
- 1% des naissances vivantes (5000 enfants par an)
- Malformation congénitale la plus fréquente chez les nouveaux-nés
- Cause majeure de morbidité dès la 1ere année de vie
- Dépistage prénatal grâce à l'échographie fœtale
- Amélioration de la prise en charge médicale et chirurgicale
- Devenir Neuro-développemental

Anomalies chromosomiques :

10% des cardiopathies congénitales ont une anomalie génétique associée

- aneuploïdie 90%
  Ex : T21, T18, T13 …
- microremaniements chromosomiques
  Ex: Syndrome de Di George

Cardiopathie	Anomalies chromosomiques
Interruption arche aortique	50%
CAV	50%
Tronc artériel commun	40%
Atrésie pulmonaire à septum ouvert	35%
Agénésie des valves pulmonaires	35%
Fallot	20%
CIV	20%
Malposition vasculaire	20%
Cardiopathie obstructive cœur gauche	10%
Ventricule unique	8%
Transposition des gros vaisseaux	0%
Atrésie pulmonaire à septum intact	0%



Bajolle 2009

Categories	Syndromes	Type of defects	Frequency of heart defects, %	Extracardiac congenital abnormalities
Aneuploidies	trisomy 21 Down syndrome	AVSD, VSD, ASD, TOF	45–50	characteristic facial features, hypothyroidism, intellectual disability, hypotonia, duodenal atresia, Hirschsprung disease
	45,X Turner syndrome	BAV, CoA, HLHS	30–32	short stature, gonadal dysgenesis, webbed neck, renal anomalies
	trisomy 18 Edwards syndrome	polyvalvular disease, VSD, ASD, PDA, endocardial cushion defects, left-sided lesions, DORV	80–100	growth retardation, clenched hands, rocker-bottom feet, omphalocele, severe intellectual disability
	trisomy 13 Patau syndrome	ASD, VSD, PDA, DORV, TOF, CoA	80	cleft lip/palate, microphthalmia, scalp defects, holoprosencephaly, postaxial polydactyly, growth retardation, severe intellectual disability
Large cytogenetic abnormalities	4p16.3 deletion Wolf-Hirschhorn syndrome	ASD, PS, TOF, VSD, PDA	50	Greek warrior helmet craniofacial dysmorphism, intellectual disability, feeding difficulties, seizures, urinary tract malformations, structural brain anomalies
	5p monosomy Cri-du-chat syndrome	PDA, VSD, ASD, TOF, pulmonary atresia	29	high-pitched cat-like cry, round face, hypertelorism, micrognathia, microcephaly, intellectual disability
	11q deletion Jacobsen syndrome	VSD, ASD, TA, DORV, BAV, AS, HLHS, MS, CoA	56	dysmorphic features, thrombocytopenia, pyloric stenosis, anal atresia/stenosis, annular pancreas, gut malrotation, growth retardation, intellectual disability
	chromosome 22 partial tetrasomy Inv dup (22)(q11) Cat eye syndrome	TAPVR, TOF, PS, tricuspid atresia, HLHS	50–67	coloboma, anal atresia, biliary atresia, malrotation of the gut, preauricular tags or pits, renal malformation
Genomic disorders	22q11.2 deletion DiGeorge syndrome	IAA type B, aortic arch anomalies, TA, TOF	75	thymic and parathyroid hypoplasia, hypocalcemia, immunodeficiency, dysmorphic features, palatal insufficiency, renal anomalies, learning difficulties, and psychiatric disorders
	7q11.23 deletion Williams-Beuren syndrome	SVAS, PPS	75	social personality, hypercalcemia dysmorphic features, intellectual disability
	8p23.1 deletion	AVSD, ASD, PS, TOF	75–94	congenital diaphragmatic hernia
	1p36 deletion	septal defects, PDA, CoA, TOF, cardiomyopathy	70	dysmorphic features, sensorineural hearing loss, seizures, intellectual disability, brain abnormalities
	1q21.1 deletion	CoA, IAA-type A, IAA-type B, BAV, aortopathy, VSD, TA, TGA, CoA, PDA	10–25	microcephaly, developmental delay
	1q21.1 duplication	TOF	20	macrocephaly, developmental delay
	17p11.2 deletion Smith-Magenis syndrome	septal defects, TOF, PS, PA, TAPVR	~30	dysmorphic features, failure to thrive, hypotonia, intellectual disability, sleep disturbance, self-injurious behaviors
	17p11.2 duplication Potocki-Lupski syndrome	dilated aortic root, septal defects, conduction abnormalities, BAV, HLHS	40	dysmorphic features, hypotonia, intellectual disability, autism spectrum disorder
	17p13.3 deletion Miller-Dieker syndrome	septal defects, TOF, PDA	20	cerebral agyria/pachygyria, type I lissencephaly, corpus callosum dysgenesis/agenesis, microcephaly, seizures, dysmorphic features, intellectual disability
	9q34.3 deletion Kleefstra syndrome	septal defects, PS, BAV, PDA	40	brachycephaly, synophrys, cupid-bowed upper lip, prominent jaw, hypotonia, intellectual disability, epilepsy, behavior abnormalities
	15q26qter deletion	VSD,ASD, CoA, HLHS, AS	~66	growth retardation, microcephaly, intellectual disability, congenital diaphragmatic hernia
	17q21.31 deletion	septal defects, PS, BAV	39	long face, upslanting palpebral fissures, epicanthic folds, tubular nose, large prominent ears, intellectual disability

AS = Aortic valve stenosis; DORV = double-outlet right ventricle; IAA-A/IAA-B = interruption of the aortic arch type A/B; MS = mitral stenosis; PA = pulmonary atresia; PPS = peripheral pulmonary stenosis; SVAS = supravalvular aortic stenosis; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great arteries; TS = truncus arteriosus.

Azamian, Mol Syndromol, 2016

Etude rétrospective

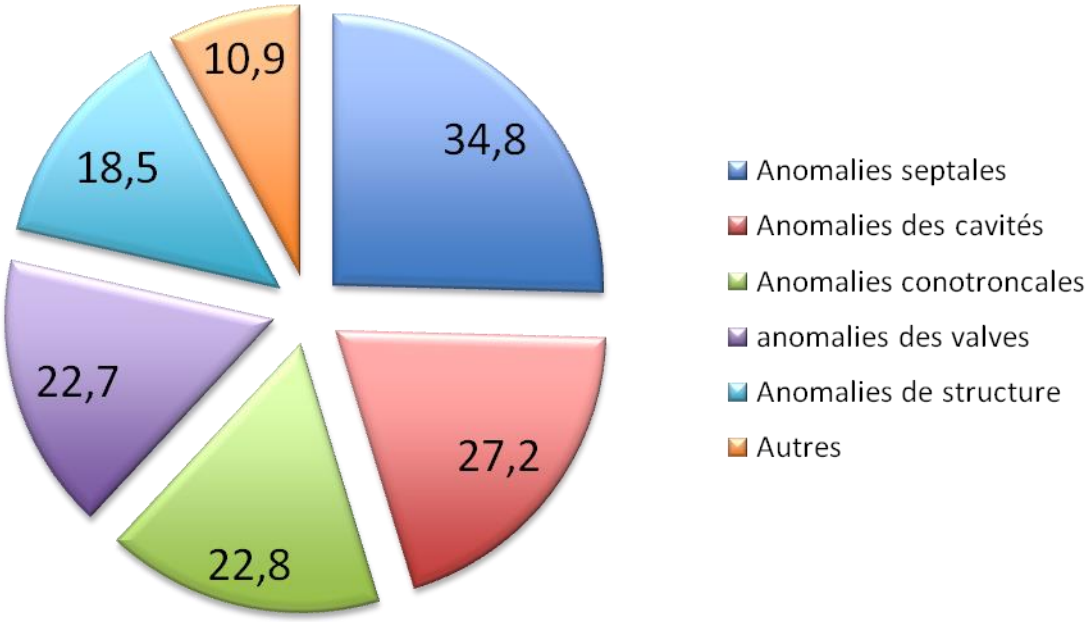
Étude rétrospective de 92 fœtus porteurs d'une cardiopathie isolée (66%) ou associée à d'autres malformations(34%)

De septembre 2013 à décembre 2015

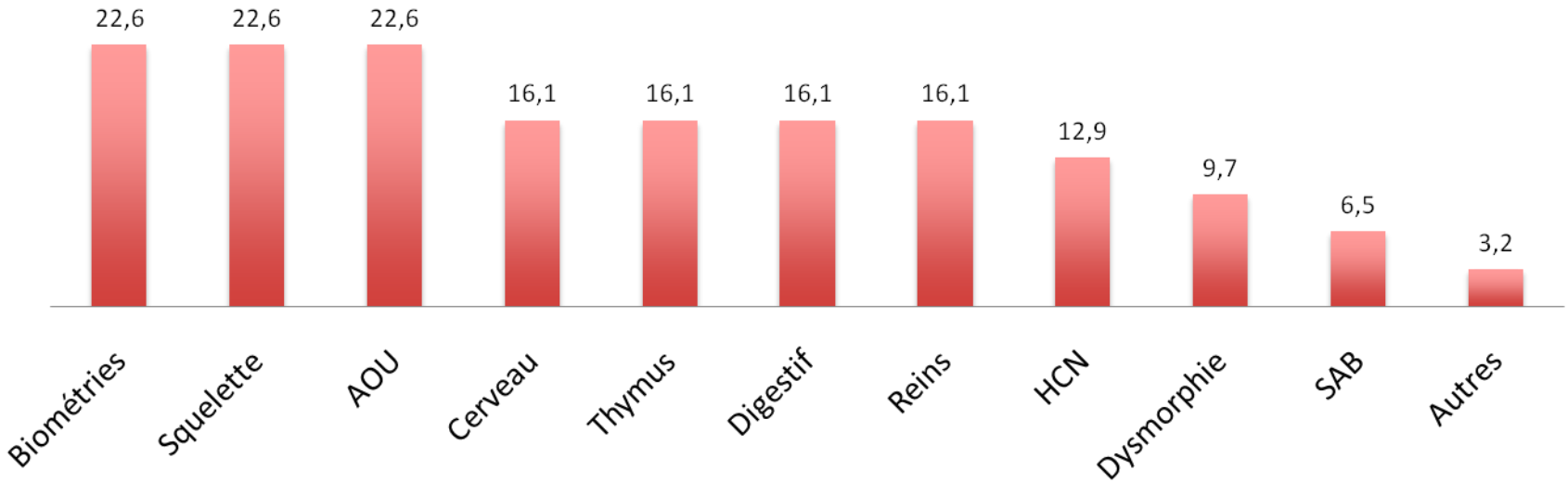
ACPA: 60 K oligonucleotide microarray (Agilent)

- Terme moyen : 21,3±5 SA
- Type de prélèvement : Amniocentèse (91,3%, n=84)
- Délai de rendu ACPA : 18,9±14,5 jours

Type de cardiopathies :



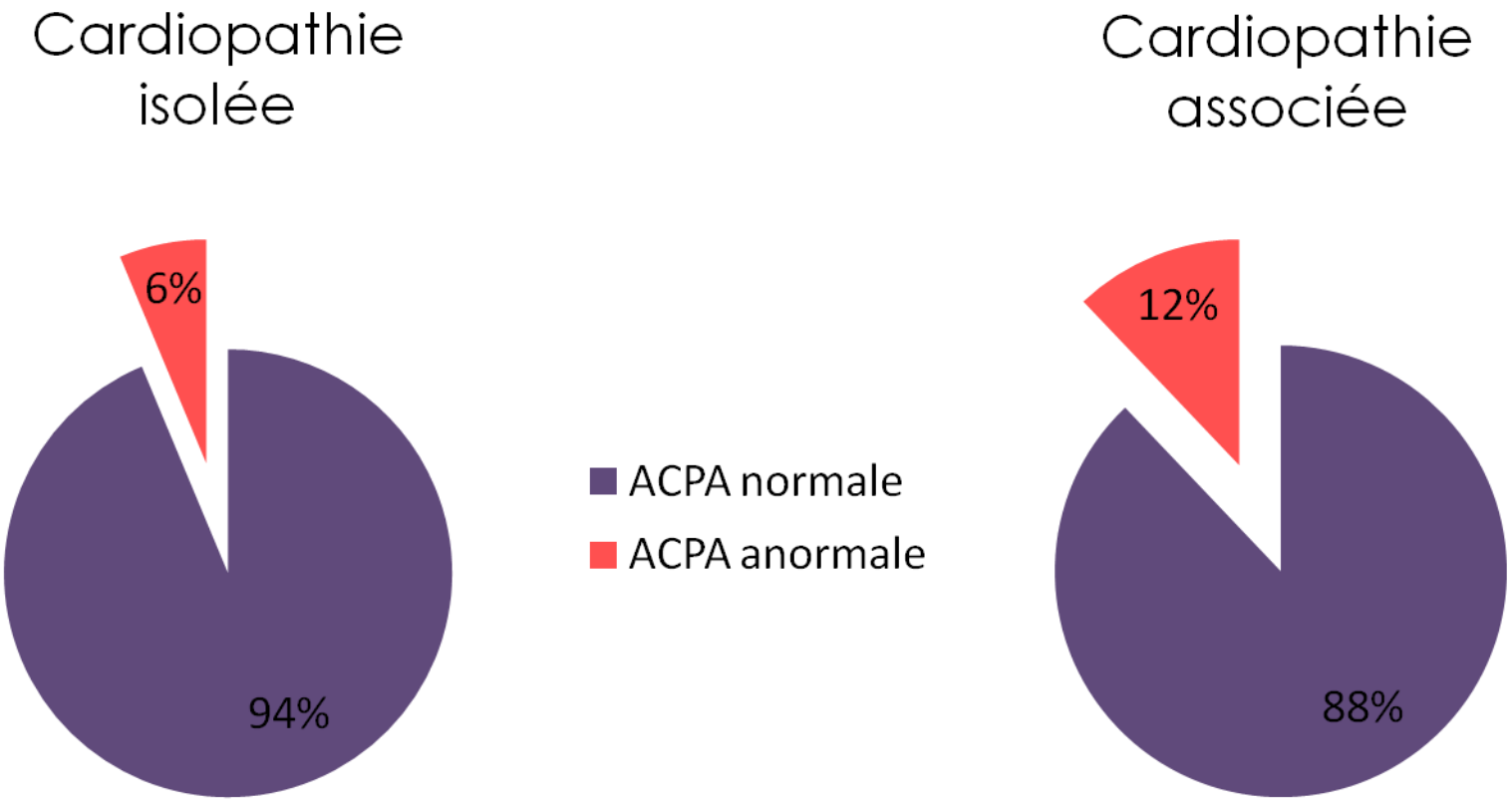
Signes d'appel échographiques associés:



Déséquilibres chromosomiques identifiés:

Formule ACPA	Taille (Mb)	Syndrome
arr 5p15.33p14.3(1-20,642,856)x3,13q32.2q34(99,290,848-115,169,878)x1	20,6 / 15,9	Monosomie 5p ; Syndrome du cri-du-chat
arr 8p23.3q24.3(1-146,364,022)x2-3,18p11.32q23(1-78,077,248)x2-3	148 / 78	Trisomie 8 au direct et 18 à la culture
arr 6q15q21(88,569,372-111,817,033)x1	23	Non rapportée
arr 11q13.5q23.2(75,219,298-113,146,143)x1 dn	38	Non rapportée
arr 8p23.1(8,130,630-11,841,901)x1	3,7	Syndrome de microdélétion 8p23.1 (*GATA4*)
arr 8p23.1(7,753,524-11,841,901)x1 dn	4	Syndrome de microdélétion 8p23.1 (*GATA4*)
arr 8p23.1(8,353,662,-11,841,901)x3 dn	3,5	Syndrome de microduplication 8p23.1 (*GATA4*)
arr 9q34.3(140,083,938-140,954,088)x1	0,87	Syndrome de Kleefstra (*EHMT1*)
arr 17p13.3(1-2,650,325)x1	2,57	Syndrome de Miller-Dieker (*LIS1*)
arr 17p13.3p13.2(2,594,489-3,727,952)x3 dn	1,13	VOUS
arr 22q11.21(18,919,942-21,440,514)x1 dn	2,5	Syndrome de DiGeorge (*TBX1*)

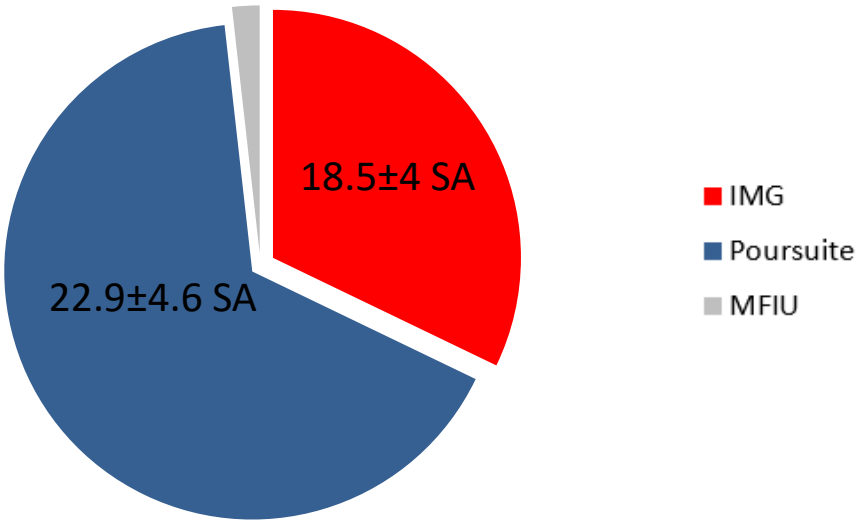
Anomalies cardiopathies associées et isolées:



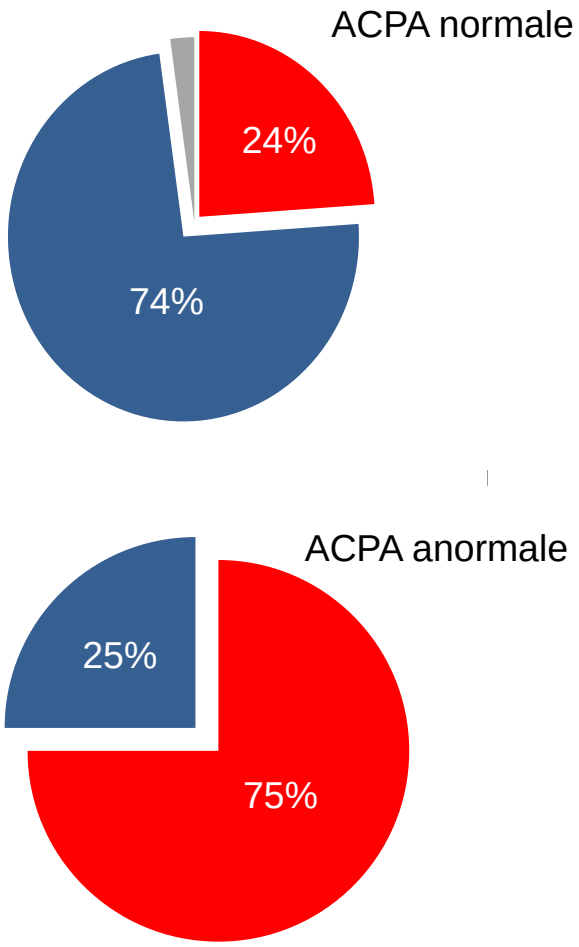
- Cardiopathies complexes
- CIV associée à d'autres malformations extracardiaques

Issues de grossesse (n=56):

En fonction du terme



En fonction du résultat de l'ACPA



Conclusions :

✓12 % d'anomalies pathogènes dépistées par l'ACPA vs 4% caryotype

✓6 % dans les cardiopathies isolées

✓Détection de micro-remaniements responsable de forme syndromique

✓ Anticipation de la prise en charge et aide pour le conseil génétique et dans le choix des parents

Meta-analyse Jansen et al., 2015 :

7.0% (95% CI, 5.3–8.6%) excluding aneuploidy and 22q11 microdeletion
3.4% (95%CI, 0.3–6.6%) in isolated CHD cases
9.3% (95%CI, 6.6–12%) when extracardiac malformations were present

Overall, 12% (95% CI, 7.6–16%) when 22q11 deletion cases were included

There was an additional yield of 3.4% (95% CI, 2.1–4.6%) for detecting variants of unknown significance (VOUS)

Merci pour votre attention