

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hansen M, Kurinczuk JJ, Bower C, and Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *N Engl J Med* 2002;346:725-30.

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**SUPPLEMENTARY APPENDIX 2. BIRTH DEFECTS OF ALL 269 INFANTS IN THE STUDY,  
ORDERED ACCORDING TO THE PRIMARY SYSTEM AFFECTED.\***

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Cardiovascular system

Tetralogy of Fallot and patent ductus arteriosus  
Tetralogy of Fallot  
Ventricular septal defect (large)  
Ventricular septal defect (moderate perimembranous)  
Ventricular septal defect (perimembranous)  
Ventricular septal defect (multiple) and patent ductus arteriosus  
Ventricular septal defect (muscular) and talipes equinovarus  
Ventricular septal defect (small muscular), distal hypospadias, and minimal chordee  
Ventricular septal defect (small perimembranous) and unspecified atrial septal defect  
Ventricular septal defect (small/moderate) and congenital dislocation of the hip (2 infants)  
Ventricular septal defect (perimembranous), unspecified atrial septal defect, patent ductus arteriosus, and possible interrupted inferior vena cava  
Unspecified ventricular septal defect, atresia of the pulmonary valve, and patent ductus arteriosus  
Unspecified ventricular septal defect, patent ductus arteriosus, interrupted aortic arch, and hypoplasia of the aortic arch  
Ventricular septal defect (moderate/muscular) and unspecified atrial septal defect (small)  
Ventricular septal defect (muscular), ostium secundum defect, absent right forearm and hand, absent fingers, hypoplastic left radius, humeral hypoplasia, finger anomalies, and Holt–Oram syndrome  
Ventricular septal defect (2 small) and unspecified atrial septal defect  
Ventricular septal defect (moderately large, perimembranous)  
Ventricular septal defect, dysmorphic/unusual facies, cleft lip and cleft soft palate, finger anomalies, and fetal alcohol syndrome  
Ventricular septal defect (small midmuscular), patent ductus arteriosus, misshapen ears, facial asymmetry, accessory toes (bilateral), and overriding sixth toe (left foot)  
Hypoplastic left-heart syndrome  
Ventricular septal defect (trivial) and mitral incompetence  
Aortic stenosis (severe) and mitral incompetence  
Bicuspid pulmonary valve (?) and aortic stenosis  
Trace aortic incompetence, mitral incompetence, patent ductus arteriosus (tiny), and infantile Marfan syndrome  
Bicuspid aortic valve, coarctation of the aorta, and posterior urethral valves  
Stenosis of pulmonary valve  
Patent ductus arteriosus  
Patent ductus arteriosus and papillary calcification of kidneys  
Common (single) ventricle, common atrioventricular canal septal defect/ventricular septal defect, stenosis of pulmonary valve, double-outlet right ventricle, total anomalous pulmonary venous return, gastrointestinal malrotation, duplication cyst, asplenia, Ivermark's syndrome, and abdominal situs inversus  
Common (single) atrium, common atrioventricular canal defect, double-outlet right ventricle, dextrocardia without situs inversus, and asplenia  
Common single ventricle, ventricular septal defects (multiple), malaligned common atrioventricular septal defect, atresia of pulmonary valve, dysplastic tricuspid valve, bilateral superior venae cavae, and superior vena cava to coronary sinus  
Unspecified atrial septal defect (2 infants)  
Ostium secundum defect, stenosis of pulmonary valve, mitral valve prolapse, mitral incompetence, congenital heart block, and patent ductus arteriosus  
Ostium secundum defect  
Artrial dilation, scoliosis, lower sternum defect, left-sided diaphragm abnormality, exomphalos, and pentalogy of Cantrell  
Vascular ring and aberrant subclavian artery

Urogenital system

Unilateral undescended testis (23 infants)  
Unilateral undescended testis and testicular atrophy  
Unilateral undescended testis and ectopic testis  
Unilateral undescended testis and congenital dislocation of the hip  
Unilateral undescended testis and vesico–ureteral reflux  
Unilateral undescended testis and coronal hypospadias (2 infants)  
Bilateral undescended testis  
Hypospadias (4 infants)  
Subcoronal hypospadias  
Glandular hypospadias (2 infants)  
Hypospadias and congenital sinus in the left thigh  
Hypospadias (unspecified), congenital chordee, and scrotalized penis  
Penoscrotal web/phimosis  
Penoscrotal web and congenital dislocation of the hip  
Scrotalized penis (partial)  
Congenital chordee and glandular hypospadias  
Congenital chordee and penoscrotal fusion  
Congenital chordee and mild shaft hypospadias  
Congenital chordee and eventration of diaphragm  
Congenital chordee and coronal hypospadias (3 infants)  
Congenital chordee and subcoronal hypospadias  
Congenital chordee, coronal glandular hypospadias, and clinodactyly  
Vesico–ureteral reflux (9 infants)  
Vesico–ureteral reflux and ventricular septal defect (small/moderate)  
Double ureter and vesico–ureteral reflux  
Hydronephrosis (bilateral) and double kidney  
Hydronephrosis and vesico–ureteral reflux  
Hydronephrosis (bilateral), mildly dilated left ureter, and ureterocele (left)  
Hydronephrosis (bilateral) and pelvic–ureteral junction obstruction

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**SUPPLEMENTARY APPENDIX 2. CONTINUED.\***

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Urogenital system (continued)  
Hydronephrosis and ectopic ureter  
Hydronephrosis and megaloureter  
Hydronephrosis (left)  
Hydronephrosis, double ureter, vesico-ureteral reflux, and ureterocele  
Multicystic dysplastic left kidney  
Ambiguous genitalia, hydronephrosis, cloaca exstrophy, and exomphalos  
Hypoplasia of the kidney (right), hydronephrosis (right), and vesico-ureteral reflux (right)  
Partial duplication of the right kidney and vesico-ureteral reflux  
Fused kidneys  
Unilateral absent kidney and vesico-ureteral reflux (right)  
Right pelvic kidney, abnormal vertebrae, and absent rib (right side)

Musculoskeletal system  
Congenital dislocation of the hip (34 infants)  
Congenital dislocation of the hip, dysmorphic/unusual facies, plagiocephaly, and short stature  
Congenital dislocation of the hip and accessory finger (right hand)  
Talipes equinovarus (11 infants)  
Talipes and genu recurvatum  
Metatarsus varus (right)  
Metatarsus adductus and tibial torsion  
Reduction deformity (right fingers/palm)  
Congenital diaphragmatic hernia  
Congenital diaphragmatic hernia and hypoplasia of lungs  
Congenital diaphragmatic hernia and dilated cerebral ventricles  
Congenital diaphragmatic hernia and hypoplasia of lungs  
Abnormal vertebrae  
Abnormal vertebrae and bilateral 13 pairs of ribs  
Craniosynostosis (2 infants)  
Shortening of right leg and curly toes

Gastrointestinal system  
Pyloric stenosis (8 infants)  
Pyloric stenosis, dysmorphic/unusual facies, and effects of fetal valproate  
Cleft lip (unilateral) (2 infants)  
Cleft lip and cleft soft palate  
Cleft lip (unilateral) with cleft palate (5 infants)  
Gastroschisis (2 infants)  
Exomphalos  
Exomphalos, ventricular septal defect (perimembranous), hypospadias (unspecified), and bifid scrotum  
Gastrointestinal malrotation and exomphalos  
Patent omphalomesenteric duct (2 infants)  
Hirschsprung's disease (2 infants)  
Duodenal web  
Meckel's diverticulum  
Meckel's diverticulum and ileal duplication cyst  
Ectopic salivary gland and skin tag over trachea  
Esophageal atresia with tracheoesophageal fistula and ventricular septal defect (moderate mid-muscular)

Central nervous system  
Encephalocele, hydrops, dysgenesis of corpus callosum, talipes equinovarus, and amniotic bands (left leg)  
Partial agenesis of the corpus callosum and hydrocephalus (unspecified)  
Dilated cerebral ventricles  
Coloboma of the optic nerve (right), microphthalmos, coloboma of the retina (right), and coloboma of the choroid and retina (left)  
Intracranial calcification and congenital cytomegalovirus  
Coloboma of lens, small notch eyelid, and abnormally shaped pupil  
Microcephaly, hydranencephaly, dysmorphic/unusual facies, ventricular septal defect (perimembranous), ectopic anus (anteriorly placed), micrognathia, congenital dislocation of the hip, finger anomalies, and Neu-Laxova syndrome (?)  
Hydrocephalus  
Holoprosencephaly, abnormal nose, cleft lip (central), and hypotelorism

Chromosomal  
Trisomy 21 (6 infants)  
Trisomy 21 and hydrops fetalis  
Trisomy 21, common atrioventricular canal, atrial septal defect/ventricular septal defect, hypoplastic right ventricle, stenosis of the pulmonary artery, and left superior vena cava to coronary sinus  
Trisomy 21, ventricular septal defects (multiple), common atrioventricular canal, atrial septal defect/ventricular septal defect, and patent ductus arteriosus  
Trisomy 21, ventricular septal defect (small perimembranous), and patent ductus arteriosus  
Trisomy 21, unspecified ventricular septal defect, unspecified atrial septal defect, and patent ductus arteriosus  
Trisomy 18, unspecified ventricular septal defects (2), congenital dislocation of the hip, finger anomalies, congenital diaphragmatic hernia, and nail hypoplasia  
Turner's syndrome (X0/XXX mosaic) and cleft soft palate (central)  
Turner's syndrome, dysmorphic/unusual facies, and pelvic-ureteral junction obstruction  
Y chromosomal anomaly  
Chromosomal anomaly 47,XXX  
Chromosomal anomaly 46,XY,del(X)(p11.3)  
Additional autosomal marker

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**SUPPLEMENTARY APPENDIX 2. CONTINUED.\***

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Metabolic

Hypothyroidism (3 infants)  
Phenylketonuria  
Glucose-6-phosphate dehydrogenase deficiency (2 infants)  
Unknown metabolic disease, talipes equinovarus, and overriding fifth toes

Other

Nevus/hemangioma (5 infants)  
Nevus/hemangioma and bronchial fistula/remnant  
Nevus/hemangioma (multiple)  
Hemangioma (right orbit/back)  
Large port-wine hemangioma  
Klippel–Trenaunay–Weber syndrome  
Hydrops fetalis  
Dysmorphic/unusual facies, ventricular septal defect (tiny/muscular), ectopic kidney, congenital dislocation of the hip, thoracic vertebral anomaly, sacral vertebral anomaly, extra ribs, abnormal ribs, and osteogenesis imperfecta  
Coloboma of right eyelid, facial cleft (lip to eye), and amniotic band syndrome (?)  
Krabbe's disease  
Angioma (right upper lip)  
Cutis aplasia  
Dysmorphic/unusual facies, finger anomalies, and hydrops fetalis  
Choanal stenosis  
Craniofacial dysmorphism  
Exophthalmos, dysmorphic/unusual facies, bulbous nose, and large cranium  
Cataract (right)  
Ptosis, exostosis (multiple), and large facial nevus  
Preauricular tags, macrostomia, facial asymmetry, and facio-auriculo-vertebral spectrum  
Rhabdomyoma (heart), scoliosis, thoracolumbar kyphosis, abnormal ribs, and tuberous sclerosis  
Glaucoma  
External angular dermoid (right eye)  
Prader–Willi syndrome  
Left-cheek lymphangioma  
Ocular albinism and congenital nystagmus

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\*Some infants have defects affecting more than one system but are listed only once. For reasons of confidentiality, we were unable to identify the mode of conception for each child. On request, however, we will exclude particular infants from the analysis and report the results of the comparison. A question mark indicates that there is some uncertainty in that part of the diagnosis. The criteria used for inclusion or exclusion of particular defects are as follows: Ventricular septal defects are coded as minor if they were specified in the report as trivial or are now closed; otherwise, they are coded as major. Isolated patent ductus arteriosus is coded as major if it was still patent at three months of age in a child born at term or at six months in a child born before term. If the ductus was ligated in a full-term infant or in a preterm infant over the chronological age of two months, it is also coded as major. Isolated ductus not meeting the above criteria is not registered. A ductus in the presence of any other congenital heart disease is always included. The majority of cases of undescended testes were only registered at the time of surgery (usually at about two years of age), regardless of when the defect was actually diagnosed. This approach ensures the cases of undescended testes that are simply retractile and descended spontaneously without surgery are excluded from the registry. Congenital dislocation of the hip is coded as a major birth defect if it was treated by abduction splinting, surgery, or both. Children with hip clicks or for whom the sole treatment prescribed was the use of double diapers are excluded. Talipes equinovarus, clubfoot, and metatarsus adductus are coded as major birth defects if they were treated by splinting or surgery; otherwise, they were not registered. Angioma and congenital nevus are included in the registry classification if they were multiple or larger than 4 cm<sup>2</sup>. They are coded as minor unless they are disfiguring or require extensive surgery, in which case they are coded as major.