Outcome of Twin Gestations After First Trimester Chorionic Villus Sampling

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Objective: To tabulate genetic results and obstetric outcomes of twin pregnancies after first-trimester chorionic villus sampling (CVS).

Methods: The study included 262 consecutive women with twin pregnancies who had first-trimester CVS between 1988 and 1998.

Results: Major indications for prenatal diagnosis included maternal age ($n = 82$), pregnancies after intracytoplasmic sperm injection ($n = 114$), or both ($n = 33$). Among 524 fetuses, 519 were sampled adequately. Cytogenetic results were incorrect because of sampling the same fetus twice in two pregnancies. In three pregnancies, contamination caused by mixed sampling made cytogenetic results uncertain. Correct genetic diagnoses were obtained in 509 fetuses, 24 of which had chromosomal abnormalities on direct preparations and four of which had monogenetic conditions. Additional invasive procedures were done on five occasions. Fifteen fetuses were terminated selectively. The total fetal loss rate was 5.5% (28 of 509). The indication for the procedure did not significantly determine the fetal loss rate. The mean $\pm$ standard deviation (SD) gestational age at birth was 35.9 ± 2.9 weeks, and the mean $\pm$ SD birth weights for twins A and B were 2429 ± 589.1 g and 2378 ± 588.5 g, respectively.

Conclusion: First-trimester CVS is an accurate means of prenatal genetic diagnosis in twins, offering early selective termination in cases of abnormal genetic results in one of the fetuses. (Obstet Gynecol 2000;96:714–20. © 2000 by The American College of Obstetricians and Gynecologists.)

Assisted reproductive technologies and ovulation induction have increased markedly the rates of twin pregnancies, frequently in women 35 years or older at delivery, which is an indication for prenatal diagnosis. The likelihood of at least one twin having a chromosomal abnormality is 1.5 times higher than in singleton pregnancies.¹

Second-trimester amniocentesis is the standard for prenatal diagnosis in twins^{2–4}; however, chorionic vil-

lus sampling (CVS) allows selective termination with a lower complication rate and less psychologic burden than if an abnormal result is encountered in one fetus of a multiple pregnancy.^{5,6} Since 1985, experienced use of CVS has proved effective, accurate, and safe for first-trimester prenatal diagnoses in singleton pregnancies.⁷ Only a few studies evaluated CVS in multiple gestations^{8–11} because of concerns about the selectivity of accessing different placental sites and processing sampled villi for reliable genetic results. Also there is the fear of incorrectly identifying genetically abnormal fetuses in cases of discordant genetic results in the first trimester. We evaluated the accuracy of the sampling procedure and genetic analysis in twin pregnancies in the first trimester and compared them with earlier data to determine feasibility and risks of CVS in twin pregnancies.

Materials and Methods

We studied 262 twin pregnancies in which CVS was done prospectively between 1988 and 1998. Follow-up was complete in all cases. Genetic counseling preceded the invasive procedures. Women were informed about the risks of chromosomal abnormalities in their pregnancies and the possibility of detecting fetal aneuploidy with CVS or amniocentesis. Patients chose whether CVS was done. Procedures were done consecutively between 9 and 13 weeks' gestation, after sonographic examination to determine viability and chorionicity of the pregnancy. In cases of monochorionic twins, the placentas were sampled twice near the cord insertion of each fetus.

Indications for CVS were chromosomal evaluation for advanced maternal age (35 years or older) ($n = 82$), pregnancies established after intracytoplasmic sperm injection ($n = 114$), pregnancies established after intracytoplasmic sperm injection in patients with advanced maternal age ($n = 33$), and chromosomal evaluation or DNA analysis for other indications, including history of

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monogenetic disease, presence of sonographic markers for fetal aneuploidy or fetal structural defects, chromosomal malformations in parents or previous pregnancies, and the psychologic indications ($n = 33$).

Chorionic villus sampling was done using ultrasound guidance with a curved linear probe, after sonographic mapping of placental implantations and cord insertions, by two operators experienced in invasive prenatal techniques. Transabdominal, transcervical, or a combination of both methods were used to obtain sufficient placental tissue. Chorionic villi were aspirated transcervically with a Portex Throphocan catheter (Laboratoire Portex 5A, Berck-Sur-Mer, France) or transabdominally with a double-needle system (outer needle 18 gauge, inner needle 20 gauge). The insertion of the outer 18-gauge trocar needle allowed for multiple chorionic aspirations in case of insufficient aspiration on the first attempt. Samples of more than 10 and 20 mg per fetus were considered appropriate for karyotyping and biochemical or DNA analysis, respectively. When discordant genetic abnormalities in dizygotic twin pregnancies were detected, a transabdominal selective termination was done within 1 week after CVS following counseling and acceptance by the parents. Under local anesthesia, potassium chloride (0.5–2 mL of 1 mEq/mL solution) was injected into or near the fetal heart until asystole was established.

Short-term chromosomal analysis was done within 72 hours.^{12,13} Cultured chromosomal preparation and amniocentesis were proposed, if necessary, to differentiate true fetal from placental mosaicism. One to 2 weeks were required for results from biochemical or DNA studies.

Information collected on each pregnancy included indications for prenatal diagnosis, maternal age, sampling route, number of instrument insertions and number of aspirations per pregnancy, results of genetic analyses, selective termination in cases of abnormal test results, preterm prelabor rupture of membranes, gestational age at delivery, mean birth weight, and neonatal outcome. Loss of one or two fetuses at less than 500 g or before 22 weeks' gestation was considered early fetal loss or spontaneous miscarriage. Fetal mortality rates included fetuses of more than 500 g or fetal death after 22 weeks' gestation, according to definitions of the Flemish Birth Registry (Studiecentrum voor Perinatale Epidemiologie) and based on World Health Organization and International Federation of Obstetrics and Gynecology criteria.^{14,15} Perinatal mortality was considered the sum of fetal and neonatal deaths in the first week of life.

Fisher exact tests were used to compare the four groups of indications for categorical variables. In cases of globally significant differences (at a significance level

of .05), two-by-two comparisons were done with a Bonferroni correction at the significance level. According to that correction, $P < .008$ was considered significant. For continuous variables, an analysis of variance model was used to investigate overall differences of the four groups, with the Tukey method for multiple comparisons to compare groups two by two.

Results

Sonographic determination of placental chorionicity found four monochorionic diamniotic (four of 262, 1.5%) and 258 dichorionic twin pregnancies (98.5%). Mean maternal ages $\pm$ standard deviation (SD) in the indication groups (chromosomal evaluation, intracytoplasmic injection, intracytoplasmic injection with advanced maternal age, and chromosomal evaluation for mixed indication) were 37.0 ± 1.8 years, 30.3 ± 2.5 years, 36.5 ± 1.8 years, and 31.3 ± 2.5 years, respectively.

Among 262 pregnancies (524 fetuses) we retrieved sufficient villi from 519 fetuses (99%). In one dichorionic pregnancy, the posterior position of the placenta and retroflexion of the uterus made a second targeted sampling impossible and the woman refused additional amniocentesis. In two other dichorionic pregnancies, maternal obesity or enlarged stimulated ovaries obstructed an aligned transabdominal approach of the placenta and resulted in aspiration of less than 10 mg of chorionic villi. A final karyotype was not established because of lack of interpretable metaphases. Only one woman opted for amniocentesis, which showed normal karyotypes for both fetuses.

The mean number $\pm$ SD of instrument insertions per pregnancy was 2.1 ± 0.42 , the mean number of aspirations was 2.5 ± 0.74 . There was no significant difference in technical aspects of the procedures between the four indication groups.

Chorionic villus sampling was done with combined transabdominal and transcervical approaches in 111 twin pregnancies (42.4%). Both placentas were sampled transabdominally in 93 cases (35.5%) and transcervically in 55 cases (21.4%).

Genetic analysis was available for 519 fetuses. Genetic diagnosis was correct in 509 cases (98.1%). In five pregnancies, prenatal cytogenetic results were incorrect or doubtful. In two cases, both biopsies were taken from the same placenta, leading to false determination of identical fetal sexes. In one of those cases, the difference in fetal sex was discovered by a second-trimester ultrasound and confirmed by additional amniocentesis. In the other case, the misdiagnosis was detected at birth when the patient delivered two healthy children of the opposite sex. In one other case, both samples contained

Table 1. Evaluation of Abnormal Cytogenetic Analysis on Direct and Long-Term Chromosomal Preparations

Type of abnormality on direct preparation	Number of abnormal direct preparations	Number of confirming long-term cultures	Number of additional invasive procedures	Outcome
Pericentric inversions	2	2/2	0	Normal
Balanced translocations	4	4/4	1	Normal
Marker chromosome	2	2/2	0	Normal (monochorionic pregnancy)
Mosaicism	3	0/3	0	Normal
Unbalanced translocation	1	1/1	1	Termination
Trisomy	7	7/7	2*	1 early fetal loss, 6 terminations
Sex chromosome abnormality	3	3/3	0	1 early fetal loss, 1 termination, 1 normal
Tetraploidy	2	1/2	1	1 termination, 1 normal
Total	24	20	5	13 normal, 2 early fetal losses, 9 terminations

* Amniocentesis at the time of the selective termination.

a mixture of villi from the two placentas resulting twice in 46,XX/46,XY fetal karyotypes. Ultrasound examination showed normal male and female infants. In each of the two remaining pregnancies 46,XX/46,XY mosaicism was detected in one of the fetuses. Normal ultrasound findings in those two pregnancies lessened the need for amniocentesis. In all cases, women delivered healthy children with normal karyotypes. Review of the ultrasound charts of those five women did not show any particular risk factor for nonselective sampling; however, all pregnancies were dichorionic and had fused placentas.

On direct chromosomal preparations, an abnormal fetal karyotype was detected in 22 twin pregnancies, affecting 24 of 519 fetuses (4.6%) (Table 1). Three cases of placental mosaicism in the direct preparation resulted in a normal karyotype in long-term culture analysis. Two additional cases of tetraploidy in the direct preparation were confined to the placenta and were normal either by long-term chorionic villus culture ($n = 1$) or by additional amniocentesis ($n = 1$). An abnormal fetal karyotype in direct and long-term preparations was observed in 17 cases (3.3%). There were four balanced translocations, two pericentric inversions, and two fetuses in a monochorionic pregnancy with a marker chromosome. Six showed trisomy 21, and one had trisomy 13. Three fetuses had numerical sex chromosome abnormalities; two had Klinefelter syndrome and one had Turner syndrome. On one occasion, an apparent complex translocation between chromosomes 6, 13, and 15 necessitated parental karyotyping and an additional confirmation amniocentesis which found 45,XY,der(13;15). Seven of those abnormal results were related to advanced maternal age (seven of 164, 4.3%), whereas four conceived by intracytoplasmic sperm injections had abnormal karyotypes (four of 223, 1.8%). Two twin pregnancies had prenatal diagnoses of Char-

cot-Marie-Tooth disease and adult polycystic kidney disease. Both were dichorionic pregnancies, and both fetuses were affected.

Data on pregnancy losses are shown in Table 2. Selective termination of one fetus was done in 11 twin pregnancies, six of which had chromosomal abnormalities on direct and long-term preparations. Although long-term villus culture showed a normal karyotype in one fetus with tetraploidy on direct preparation, and the woman was counseled about placental polyploidy in a reassuring manner, she opted for selective termination. Early second-trimester preterm prelabor rupture of membranes occurred in the precervical gestational sac of two twin pregnancies, so the two anhydramnic fetuses were selectively terminated to achieve a better outcome for the remaining one. In two additional cases, fetal termination was done once for cervical incompetence and once for psychologic distress. Two twin pregnancies were terminated completely, in which both fetuses were affected by a chromosomal abnormality (47,XXY and 47,XX+21) or Charcot-Marie-Tooth disease.

Two women opted to continue pregnancies despite fetal abnormalities detected by CVS. In one, both fetuses were affected by adult polycystic kidney disease, and in the second, one fetus had Klinefelter syndrome.

Sixteen of the remaining 509 fetuses (nine pregnancies) were lost before the 22nd week of gestation (3.1%). Two fetuses with 45,X and trisomy 13 karyotypes miscarried within 10 days after CVS. Seven pregnancies were lost completely before the 22nd week of gestation, one of which was the result of early deteriorating twin-twin transfusion syndrome.

After 22 weeks, three pregnancies were complicated by preterm prelabor rupture of membranes and were lost completely. One fetus died in each of six other pregnancies. Two of those had severe congenital mal-

Table 2. Fetal Loss Rates in Relation to Indication for Chorionic Villus Sampling

	<i>n</i> (%)	Pregnancies by intracytoplasmic sperm injection (<i>n</i> = 114)	Pregnancies with advanced maternal age (<i>n</i> = 82)	Pregnancies by intracytoplasmic sperm injection in patients with advanced maternal age (<i>n</i> = 33)	Patients with other indications (<i>n</i> = 33)
Termination					
Single fetus	11	1	6	2	2
Total pregnancy	2	1	0	0	1
Early fetal demise ≤22 weeks					
Single fetus	2	0	1	0	1
Total pregnancy	7	2	3	1	1
Fetal loss after 22 weeks					
Single fetus	6	2	4	0	0
Total pregnancy	3	1	1	0	1
Total fetal loss	28 (5.5)	8 (3.6)	13 (8.2)	2 (3.1)	5 (8.0)
Neonatal loss					
Single neonate	0	0	0	0	0
Both neonates	3	1	0	0	2
Total	6 (1.2)	2 (0.9)	0	0	4 (7.0)

formations; one had a major lumbosacral neural tube defect with associated hydrocephaly, the other had agenesis of the corpus callosum and a cardiac defect. The fetal loss rate after 22 weeks' gestation was 2.4% (12 of 493).

The total spontaneous fetal loss rate, defined as fetal loss after CVS until birth was 5.5% (28 of 509). After exclusion of the congenital malformations, (twin-twin transfusion syndrome, two severe congenital malformations, 45,X, and trisomy 13) the corrected total fetal loss rate was 4.3% (22 of 509). Six neonates died because of early preterm delivery after preterm prelabor rupture of membranes at 22, 25, and 26 weeks (1.2%). The infant survival rate after first-trimester CVS in twin pregnancies was 90.6% (475 of 524). When the CVS procedures were done for advanced maternal age or other indications, total fetal loss rates were 8.2% and 8.0%, respectively. Pregnancies by intracytoplasmic sperm injection had an insignificantly lower fetal loss rate after CVS (3.6%), even with advanced maternal age (3.1%). Combining transcervical and transabdominal routes resulted in a fetal loss rate of 2.7%. Transcervical or transabdominal CVS of both fetuses resulted in miscarriage rates of 3.6% and 4.3%, respectively ($P > .05$).

Perinatal outcome was calculated for 253 pregnancies or 493 fetuses, after excluding four terminated pregnancies, 11 selective terminations, and 16 early miscarriages. The mean $\pm$ SD gestational age at delivery was 35.9 ± 2.9 weeks (range 23–41 weeks). The mean birth weights $\pm$ SD for twins A and B were 2429 ± 589 g (range 550–4030 g) and 2378 ± 589 g (range 450–3620 g), respectively. Preterm delivery (no more

than 37 weeks) occurred in 176 pregnancies (69.6%), whereas early preterm delivery (no more than 33 weeks) happened in 35 twin pregnancies (13.8%). There were no significant differences in mean gestational age at delivery, preterm and early preterm delivery, and low-birth-weight neonates according to procedure indication.

Discussion

Different authors^{8–11} have evaluated feasibility and risks of CVS in twin pregnancies; however, the samples in those studies were relatively small, ranging from 65⁸ to 161.¹⁰ Our findings present additional data in favor of first-trimester prenatal diagnosis by CVS showing its safety, accuracy, and advantage for early selective termination.

Indications for prenatal diagnosis in twin pregnancies are similar to those for singletons. Having two fetuses doubles the risk of aneuploidy.¹ Meyers et al¹⁶ calculated that the risk of at least one aneuploid twin at term at the maternal age of 31 years was comparable to the risk of an aneuploid singleton term pregnancy at the maternal age of 35 years. Hence, some centers offer invasive prenatal testing in twin pregnancies at earlier maternal ages. At our center, the term advanced maternal age is applied to all gravidas who will be at least 35 years old at the expected delivery date. Cytogenetic evaluation of twin pregnancies after intracytoplasmic sperm injection was the most important indication for prenatal diagnosis in our study because of the higher frequency of sex chromosome abnormalities¹⁷ in sperm

Table 3. Reported Outcomes of Chorionic Villus Sampling in Twin Pregnancies

	Wapner et al ¹⁰	Pergament et al ⁹	Brambati et al ⁸	Present study	Total
Year published	1993	1992	1991	2000	
Number	161	126	65	262	614
Fetal loss before 22 weeks	14/309 (4.5%)	5/244 (2.0%)	2/120 (1.7%)	16/509 (3.1%)	37/1182 (3.1%)
Total fetal loss rate	15/309 (4.8%)	10/244 (4.1%)	2/120 (1.7%)	28/509 (5.5%)	55/1182 (4.6%)

of men with oligoasthenoteratospermia. A prospective follow-up study showed a slight increase in de novo chromosomal aberrations (1.66%) and a higher frequency of transmitted chromosomal aberrations in children born after intracytoplasmic sperm injection.¹⁸

More than 98% of the twin pregnancies in our study were dichorionic, as determined by the initial ultrasound examination. In a normal twin population about 80% would be dichorionic and the remaining 20% monochorionic. Our population was biased by the high number of pregnancies by assisted reproductive techniques (147 of 262) and advanced maternal age (82 of 262), both of which favor dizygotic twinning.

Chorionic villus sampling in twin gestations was rarely unsuccessful (five of 524 fetuses). Failure to retrieve sufficient villi was associated with extreme retroflexion of the uterus, maternal obesity, and enlarged hyperstimulated ovaries. Some of those failures could have been avoided by postponing the procedure or doing amniocentesis later in gestation. However, one of those women declined further prenatal diagnosis.

Chorionic villus sampling in twin pregnancies entails a risk of 4–6% of samples being mixed, which is higher than in amniocentesis.^{9,10,19} We had two cases of erroneous sampling and three cases of tissue mixing in the first 104 twin pregnancies. All five had fused dichorionic placentas. Although operators had some experience with both sampling methods in singleton pregnancies, approaching a fused dichorionic placenta was part of a new learning curve. Wijnberger and coworkers²⁰ substantiated a learning curve for CVS and showed that safety and success of a procedure was strongly related to number of procedures done by an operator. That learning curve is probably more important when CVS is used for prenatal diagnosis in twin pregnancies. We initially believed that transcervical sampling of both fetuses caused a higher risk of tissue contamination,¹¹ but in two additional cases of cross-contamination, both fetuses were sampled transabdominally. There were no cross-contamination cases in the last 158 twin pregnancies. Individualization of each fetus with special notice of intertwin positions and relationships was the most important issue in prenatal diagnosis in multiple preg-

nancies. Umbilical cord insertion onto the chorionic plate might serve as a landmark. Concordant abnormal genetic results in dichorionic fetuses of the same gender are extremely rare, with the calculated probability depending on the type of abnormality and were .0001% and .017%¹⁹ for generalized or placentally confined mosaicism, respectively. That condition should always prompt the question of erroneous or mixed sampling. Repeat sampling by CVS or additional amniocentesis is necessary to elucidate that controversy.^{21,22} Additional cytogenetic and DNA polymorphism studies should be done when the sexes are identical and the twins are concordant for a karyotype anomaly.¹⁹ Inconclusive results after first-trimester prenatal diagnosis by CVS (by direct or long-term culture analysis) must be determined by additional amniocentesis. Although combining the two procedures is rarely needed, it probably increases the risk of miscarriage.

Most genetic problems in dichorionic twin pregnancies are discordant and thus affect only one fetus. Previously they were managed by termination or continuation of the entire pregnancy without interference. Expectant management might still be preferable to invasive approaches when death of a karyotypically abnormal fetus is inevitable.²³ However, Malone and coworkers²⁴ found that an anomalous fetus in a twin gestation significantly increased the risk of preterm delivery, frequency of cesarean, and perinatal mortality rates compared with normal twin gestations. Therefore, couples should be informed that early selective termination of the affected fetus in cases of discordant results in dichorionic twin pregnancies carries a small risk of complete pregnancy loss compared with selective termination after diagnosis by amniocentesis in the second trimester.^{5,6,23,25,26}

The fetal loss rate of 5.5% in this study matches well the data from the literature^{8,9,10,11} as presented in Table 3. Aytoz et al²⁷ found that the fetal loss rate after CVS in 111 twin pregnancies by intracytoplasmic sperm injections did not differ statistically significantly from that of a control population. Number of fetal losses were comparable to those after amniocentesis in twin pregnancies.^{2,3,4,10} There are still high spontaneous loss rates

in twin pregnancies after viability is established by ultrasound. In a 5-year prospective study of 137 sonographically identified twin pregnancies at a mean gestational age of 10.1 weeks, a complete pregnancy loss rate of nearly 11% was found.²⁸ A fetal loss rate of 3.2% was found in twin pregnancies after a normal ultrasound examination between 14 and 20 weeks' gestation.³ Advanced maternal age was considered a factor in increased fetal loss after CVS in singleton pregnancies.²⁹ Pergament and coworkers⁹ found no increase in procedurally related pregnancy losses after CVS for advanced maternal age in singleton and twin pregnancies. In our data there was an insignificant trend toward higher rates of fetal loss in the older maternal age group. Chorionic villus sampling in intracytoplasmic sperm injection twin pregnancies was associated with a low risk of pregnancy complications,²⁷ which should make CVS an acceptable alternative for amniocentesis even in twin pregnancies after infertility treatment.

References

- Rodis JF, Egan JF, Craffey A, Ciarleglio L, Greenstein RM, Scorza WE. Calculated risk of chromosomal abnormalities in twin gestations. *Obstet Gynecol* 1990;76:1037-41.
- Pruggmayer MR, Jahoda MG, Van der Pol JG, Baumann P, Holzgreve W, Karkut G, et al. Genetic amniocentesis in twin pregnancies: Results of a multicenter study of 529 cases. *Ultrasound Obstet Gynecol* 1992;2:6-10.
- Ghidini A, Lynch L, Hicks C, Alvarez M, Lockwood C. The risk of second-trimester amniocentesis in twin gestations: A case-control study. *Am J Obstet Gynecol* 1993;169:1013-6.
- Ko T, Tseng L, Hwa I, Lu P, Cheug Y, Hsieh F. Second trimester genetic amniocentesis in twin pregnancies. *Int J Gynaecol Obstet* 1998;61:285-7.
- Lynch L, Berkowitz R, Stone J, Alvarez M, Lapinski R. Preterm delivery after selective termination in twin pregnancies. *Obstet Gynecol* 1996;87:366-9.
- Evans M, Goldberg J, Dommergues M, Wapner R, Lynch L, Dock B, et al. Efficacy of second trimester selective termination for fetal abnormalities: International collaborative experience among the world's largest centers. *Am J Obstet Gynecol* 1994;171:90-4.
- WHO/PAHO consultation on chorionic villus sampling. Evaluation of chorionic villus sampling safety. *Prenat Diagn* 1999;19:97-9.
- Brambati B, Tului L, Lanzani A, Simoni G, Travi M. First trimester genetic diagnosis in multiple pregnancy: Principles and potential pitfalls. *Prenat Diagn* 1991;11:767-74.
- Pergament E, Schulman JD, Copeland K, Fine B, Black SH, Ginsberg NA, et al. The risk and efficacy of chorionic villus sampling in multiple gestations. *Prenat Diagn* 1992;12:377-84.
- Wapner RJ, Johnson A, Davies G, Urban A, Morgan P, Jackson L. Prenatal diagnosis in twin gestations: A comparison between second-trimester amniocentesis and first trimester chorionic villus sampling. *Obstet Gynecol* 1993;82:49-56.
- De Catte L, Liebaers I, Foulon W, Bonduelle M, Van Assche E. First trimester chorionic villus sampling in twin gestations. *Am J Perinatol* 1996;13:413-7.
- Gibas LM, Grujic S, Barr MA, Jackson LG. A simple technique for obtaining high quality chromosome preparations from chorionic villus samples using FdU synchronization. *Prenat Diagn* 1987;7:323-7.
- Yu MT, Yu CY, Yu CX, Maidman J, Warburton D. Improved methods of direct and cultured chromosome preparations from chorionic villus samples. *Am J Hum Genet* 1986;38:576-81.
- World Health Organization. Recommended definition, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta Obstet Gynecol Scand* 1977;56:247-53.
- International Federation of Gynecology and Obstetrics. Standing Committee on Perinatal Mortality and Morbidity. Report of the Committee following a workshop on monitoring and reporting perinatal mortality and morbidity. Geneva, Switzerland: International Federation of Gynecology and Obstetrics, 1982.
- Meyers C, Adam R, Dungan J, Prenger V. Aneuploidy in twin gestations: When is maternal age advanced? *Obstet Gynecol* 1997;89:248-51.
- Moosani N, Pattinson HA, Carter MD, Cox DM, Rademaker AW, Martin RH. Chromosomal analysis of sperm from men with idiopathic infertility using sperm karyotyping and fluorescence in situ hybridization. *Fertil Steril* 1995;64:811-7.
- Bonduelle M, Camus M, De Vos A, Staessen C, Tournaye H, Van Assche E, et al. Seven years of intracytoplasmic sperm injection and follow-up of 1987 subsequent children. *Hum Reprod* 1999;14(Suppl 1):243-64.
- van den Berg C, Braat A, Van Opstal D, Halley DJ, Kleijer WJ, den Hollander NS, et al. Amniocentesis or chorionic villus sampling in multiple gestations? Experience with 500 cases. *Prenat Diagn* 1999;19:234-44.
- Wijnberger LDE, van der Schouw YT, Christiaens GCML. Learning in medicine: Chorionic villus sampling. *Prenat Diagn* 2000;20:241-6.
- Brandenburg H, van der Meulen JH, Jahoda MG, Wladimiroff JW, Niermeijer M, Habbema JD. A quantitative estimation of the effect of prenatal diagnosis in dizygotic twin pregnancies in women of advanced maternal age. *Prenat Diagn* 1994;14:243-56.
- Christiaens GC, Oosterwijk JC, Stigter RH, Deutz-Terlouw PP, Knepper ALJ, Bakker E. First-trimester prenatal diagnosis in twin pregnancies. *Prenat Diagn* 1994;14:51-5.
- Sebire NJ, Snijders RJM, Santiago C, Papapanagiotou G, Nicolaides K. Management of twin pregnancies with fetal trisomies. *Br J Obstet Gynaecol* 1997;104:220-2.
- Malone FD, Craigo SD, Chelmow D, D'Alton ME. Outcome of twin gestations complicated by a single anomalous fetus. *Obstet Gynecol* 1996;88:1-5.
- Brambati B, Formigli L, Mori M. Multiple pregnancy induction and selective fetal reduction in high genetic risk couples. *Hum Reprod* 1994;9:746-9.
- De Catte L, Camus M, Bonduelle M, Liebaers I, Foulon W. Prenatal diagnosis by chorionic villus sampling in multiple pregnancies prior to fetal reduction. *Am J Perinatol* 1998;15:339-43.
- Aytoz A, De Catte L, Camus M, Bonduelle M, Van Assche E, Liebaers I, et al. Obstetrical outcome after prenatal diagnosis in pregnancies obtained after intracytoplasmic sperm injection. *Hum Reprod* 1998;13:2958-61.
- Grobman WA, Peaceman AM. What are the rates and mechanisms of first and second trimester pregnancy loss in twin pregnancies? *Clinical Obstet Gynecol* 1998;41:37-45.
- Jahoda MGJ, Brandenburg H, Reus A, Cohen-Overbeek TE, Wladimiroff JW, Los FJ, et al. Transcervical (TC) and transabdominal (TA) chorionic villus sampling for prenatal diagnosis in Rotterdam: Experience with 3611 cases. *Prenat Diagn* 1991;11:559-61.

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