Maternal and Fetal Sequelae of Anticoagulation During Pregnancy

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Review of published cases of pregnancies in which coumarin derivatives or heparin were administered demonstrates that use of either class of anticoagulant carries substantial risks.

Of 418 reported pregnancies in which coumarin derivatives were used, one-sixth resulted in abnormal liveborn infants, one-sixth in abortion or stillbirth and, at most, two-thirds in apparently normal infants. In addition to the expected hemorrhagic complications, fetal effects of coumarin derivative administration include a specific embryopathy and central nervous system abnormalities. All available cases (including unpublished ones) of warfarin embryopathy and central nervous system abnormalities following gestational exposure to coumarin derivatives are reviewed, various complications are tabulated, critical periods of teratogenesis are discussed and possible mechanisms proposed.

The use of heparin during gestation does not result in a significantly better outcome of pregnancy. In 135 published cases, the infants in one-eighth were stillborn, in one-fifth premature (a third of whom died) and, again at most, in two-thirds apparently normal.

Because of the substantial risks of both classes of anticoagulants, and the inherent risks of pregnancy complicated by the indications for anticoagulation, prevention of pregnancy is usually indicated. If pregnancy occurs, a relatively normal outcome can be anticipated in about two-thirds of the pregnancies regardless of the anticoagulant used. Heparin does not appear to be a clearly superior alternative to coumarin derivatives.

Administration of coumarin derivatives to women during the first trimester of pregnancy causes a specific constellation of malformations in some of the offspring, known as the warfarin embryopathy or fetal warfarin syndrome [1-6]. In addition, use of coumarin derivatives by the mother at any time during pregnancy may increase the risk of central nervous system anomalies in the fetus [7-11]. In an attempt to establish teratogenic risk, we have reviewed the literature on the use of coumarin-related vitamin K antagonists during pregnancy [1-3,7,9-117]. This review allows us to estimate the relative frequencies of warfarin embryopathy and central nervous system anomalies following the use of coumarin derivatives, as well as other gestational complications in such pregnancies. We have also reviewed, for comparison, the outcome of pregnancies in which heparin (the primary alternative to coumarin derivatives for anticoagulation) was used [22,23,25,30,40,63,66,68,72,82,93,94,100,118-134]. In addition, follow-up information on many of the cases of warfarin embryopathy, data relating to critical periods of exposure, and possible mechanisms of production of the teratogenic effects of coumarin derivatives are summarized.

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METHODS AND RESULTS

Warfarin Embryopathy (Fetal Warfarin Syndrome). Shaul and Hall [6] summarized the abnormalities seen in 11 patients with exposure to warfarin during gestation and suggested that the most constant features were nasal hypoplasia and stippled epiphyses. We are now aware of an additional 13 such patients; five of these cases are as yet unpublished. We believe that the minimal criteria for designation of a case as warfarin embryopathy are exposure to coumarin derivatives* during the first trimester and the presence of either characteristic nasal hypoplasia or stippled epiphyses. Other features (including central nervous system and eye abnormalities) originally thought to be part of this syndrome [6,8] are more likely due to exposure during the second and third trimester.

The 24 cases known to us are summarized in **Tables I and II.** In these tables, the cases are listed by first author of the initial publication or communicating health professional. All weights and lengths have been converted to grams and centimeters, whereas the weeks of exposure are our best estimate of the *gestational* weeks during which a coumarin derivative was administered, regardless of the way in which time of exposure was originally reported.

As previously reported in the 11 original cases, the only consistent feature is nasal hypoplasia and depression of the bridge of the nose resulting in a flattened upturned appearance. In severe cases, the nose appears actually sunken into the face. A deep groove between the alae nasi and the tip of the nose is often present, probably secondary to undergrown cartilage. The nares and air passages are usually small resulting in neonatal respiratory distress secondary to upper airway obstruction in about half of the patients. True choanal stenosis was documented in only four subjects.

Stippling in uncalcified epiphyseal regions, and in certain cartilages and soft tissues secondary to abnormal calcification was present in all but two patients when looked at for an appropriate age. (Stippling may not be evident after the first year of life.) The stippling, which is seen roentgenographically, occurs primarily in the axial skeleton, at the proximal femurs, and in the calcanei. Its distribution is distinguishable from the stippling seen in phenotypically similar genetic disorders such as rhizomelic chondrodysplasia punctata (in which stippling is most marked in the knees, elbows and wrists) and Conradi-Hunermann syndrome (in which stippling is asymmetric).

No other findings in the cases of warfarin embryopathy are as frequent. In eight of 20 patients (40 per cent) in whom adequate information is available, birth-weight was less than the 10th percentile for gestational age. Four of 24 affected subjects (17 per cent) had significant eye abnormalities (i.e., blindness, optic atrophy and microphthalmia); all four were exposed to coumarin derivatives in all three trimesters. In 12 of 24 (50 per cent) subjects, variable degrees of hypoplasia of the extremities were reported, ranging from severe rhizomelic dwarfing (Case 4) to dystrophic nails and shortened fingers (Cases 2,5,6,7,8,10,12,13,16 and 17).

Follow-up information is available on 17 of the 24 subjects. Some patients demonstrate catch-up growth in weight and height. However, the nose may show no apparent catch-up and has remained small and sunken into the face in severely affected cases. Calcific stippling is incorporated into epiphyses and has not resulted in asymmetric growth, but it may account for the scoliosis in four instances (with hemivertebrae in Case 17 [117]).

Only an estimate of development in patients with warfarin embryopathy is possible since various methods of evaluation (ranging from clinical assessment to formal psychometrics) were utilized. Significant developmental retardation occurred in five of 16 (31 per cent) patients for whom there is adequate information: three are mildly retarded whereas two are moderately or severely retarded. All patients with mental retardation were exposed to coumarin derivatives in the last two trimesters as well as the first trimester. Other noted sequelae include death (five of 24, 21 per cent), scoliosis (four of 24, 17 per cent), blindness (three of 24, 12 per cent, all of whom were also developmentally delayed), deafness (three of 24, 12 per cent), congenital heart disease (two of 24, 8 per cent) and seizures (one of 24, 4 per cent). Over-all, one-half (12 of 24) apparently have no severe disability.

Analysis of these 24 cases has allowed us to recognize a specific time of embryologic exposure (a 'critical period') which is necessary for the production of embryopathic manifestations. In **Figure 1** each case of warfarin embryopathy is shown with the bar representing the best estimate of the weeks of gestation during which exposure to coumarin derivatives occurred. All 24 patients in whom warfarin embryopathy was demonstrable were exposed between the sixth and ninth week of gestation; there is no other common time of exposure.

The findings in the 24 cases summarized here support a causal relationship between exposure to an oral anticoagulant during a specific period of gestation and the presence of specific malformations at birth.

Central Nervous System Abnormalities Following Exposure to Coumarin Derivatives During Gestation. In 1947, von Sydow [13] described a child exposed to an oral anticoagulant throughout gestation in whom hydrocephalus developed neonatally. He and subsequent investigators have assumed that the mechanism of

* For our purposes, coumarin derivatives are all oral vitamin K antagonists including not only hydroxycoumarin derivatives (such as warfarin (Coumadin), dicumarol, phenprocoumon and acenocoumarol) but also indan-1,3-dione derived drugs (including phenindione, diphenadione and anisindione) which, although not strictly congeners of coumarin, are therapeutically, functionally and structurally related [135a]. The term *warfarin embryopathy*, although not completely accurate, is used here because of historic precedence and general usage.

TABLE I Summary of Maternal, Pregnancy and Neonatal History in 24 Cases of Warfarin Embryopathy

Case	Reference	Anticoagulant	Daily Dose (mg)	Exposure (wk of gestation)	Indications	Pregnancy/Delivery/ Placenta	Birth Length (cm)	Birth Weight (g)	Sex
1	DiSaia [1,45,73]	Warfarin	. . .	0–26, 28–36	Rheumatic mitral valve replacement	39 wk/midforceps/ small and infarcted	47	2,275	F
2	Kerber [53,105]	Warfarin	7.5	0–32	Rheumatic mitral valve replacement	39 wk/low forceps/ normal	. . .	2,810	M
3	Tejani [76]	Warfarin	5–10	0–35	Rheumatic mitral valve replacement	36 wk/transverse lie: C-section/normal	. . .	2,950	F
4	Becker [1]	Warfarin	7.5	0–35	Rheumatic aortic valve replacement	35 wk/breech/	23.5 (crown-rump)	1,370	M
5	Shaul [3]	Warfarin	2.5–5	0–35	Rheumatic mitral stenosis	35 wk/fetal brady-cardia: C-section/ normal	43	1,800	M
6	Barr [89]	Warfarin	. . .	0–15	Organic heart disease	15 wk/saline abortion/ eccentric insertion of cord	18.3	109	F
7	Pettifor [2,151]—Case 1	Phenin-dione	. . .	0–41	Rheumatic aortic valve replacement	42 wk/	. . .	3,200	M
8	Pettifor [2]—Case 2	Warfarin	5–7.5	0–38	Rheumatic mitral valve replacement	38 wk/low forceps/	. . .	2,500	M
9	Pettifor [2]—Case 3	Warfarin	7.5–10	0–38	Rheumatic valvotomy	41 wk/	. . .	3,300	F
10	Holmes [110]	Warfarin	7.5–10	0–8	Thrombophlebitis	Term/uncomplicated/	47.5	2,430	F
11	Pauli—A [95,98, 106]	Warfarin	7.5–10	6–32	Thrombophlebitis with pulmonary embolism	32 wk/uncomplicated/ single umbilical artery	44	1,720	F
12	O'Connor [115]	Warfarin	. . .	0–14	Thrombophlebitis with multiple pulmonary emboli	41 wk/	. . .	. . .	. . .
13	Johnson [112]	Warfarin	10–15	6–32	Thrombophlebitis		. . .	3,790	M
14	Richman [96]	Warfarin	. . .	0–28	Thrombophlebitis	36 wk/uncomplicated/	48	2,770	F
15	MacLeod [113]	Warfarin	5	0–35	Mitral valve prosthesis and cerebral embolism from leg	40 wk/uncomplicated/ single umbilical artery	. . .	2,570	F
16	Fourie [83]	Warfarin	5	0–37	Rheumatic mitral and aortic valve replacement	38 wk/induced, forceps/	48	2,840	F
17	Pauli—C [117]	Warfarin	7.5	0–31	Thrombophlebitis	37 wk/weight loss, breech, C-section/	45.5	2,610	F
18	Vanlaeys [104]	Acenocou-marin	. . .	0–26	Aortic and mitral valve prostheses	Term/	. . .	. . .	M
19	Raivio [102]—Case 2	Warfarin	. . .	0–35	Rheumatic mitral valve replacement and acute myo-cardial infarction	37 wk/asphyxia: C-section/	44	2,150	M
20	Lutz [108]—Case 17	Warfarin	. . .	0–8	Valve prosthesis	Term/	. . .	. . .	M
21	Robinson [107]	Warfarin	6–8	0–38	Deep vein thrombosis	38 wk/low forceps/	. . .	. . .	M
22	Harrod [110]—Case 1	Warfarin	10	9–29	Thrombophlebitis		. . .	3,690	M
23	Harrod [110]—Case 2	Warfarin	12.5	6–24	Thrombophlebitis		. . .	3,280	F
24	Madden [114]	Warfarin	. . .	0–35	Pulmonary embolism	Term/	. . .	3,675	F

TABLE II Summary of Clinical Characteristics of 24 Cases of Warfarin Embryopathy

Case	References	Died	Skeletal	Nose	Breathing Problem	Eye	Development	Other
1	DiSaia [1,45,73]		Stippling: cervical vertebrae, sacrum, femurs; kyphoscoliosis, prominent occiput	Flat nose, absent septum, small nares, ectopic lacrimal duct	Nasal obstruction as neonate	Bilateral optic atrophy; blind	Mild retardation	
2	Kerber [53,105]	+	Stippling: ?; scoliosis, vertebral posterior wedging, subluxation of C_1 on C_2; short limbed, short clubbed digits, broad fingers; basilar skull invagination; fibrovascular dysplasia of bone	Marked hypoplasia, choanal stenosis, severely sunken into face	Respiratory distress as neonate	None noted	Moderate retardation	Seizures, deafness, focal cerebral atrophy, disorientation of gyral patterns, olfactory tract shortening
3	Tejani [76]		Occipital bone abnormality	Hypoplastic nasal cartilage		Microphthalmia; probably blind	Severe retardation	Lowset ears, high palate, persistent ductus arteriosus, occipital meningomyelocele, hydrocephalus postmeningitis
4	Becker [1]	+	Stippling: vertebrae, sacrum, long bones; severe shortening and mild asymmetry of long bones; short broad fingers	Hypoplastic nasal bridge, severely sunken into face		Left lens opacity	(Died)	Poorly developed ears, contractures of right elbow and wrist
5	Shaul [3]		Stippling: cervical vertebrae, sacrum, trochanter and calcanei; prominent occiput, short, broad hands	Hypoplastic bridge and alae nasi, choanal stenosis	Respiratory distress as neonate, relieved by oral airway	Normal exam	Normal	Hypotonic
6	Barr [89]	+	Stippling: ?; small distal phalanges	Broad base, flattened upturned nose		Large, prominent eyes, small eyelids, hyperteloric	(Died)	Large, broad tongue
7	Pettifor [2,151] —Case 1		Stippling: vertebrae, sacrum and carpals; short neck, hypoplastic distal phalanges with radial deformity of index finger	Hypoplasia	Moderate distress	Right optic atrophy and blindness; hypertelorism	Mild retardation	Crinkly ears, large tongue, short neck, sparse hair in frontal region, small fingernails
8	Pettifor [2] —Case 2		Stippling: vertebrae, sacrum, cuboid,	Severe hypoplasia,	Apnea at birth, needed oral	Normal exam	Normal	Small fingernails

Continued

Table II (Cont'd) Summary of Clinical Characteristics of 24 Cases of Warfarin Embryopathy

Case	References	Died	Skeletal	Nose	Breathing Problem	Eye	Development	Other
			carpals, phalanges and calcanei; 3rd fontanelle; small terminal phalanges in hands and feet	narrow nasal passages	airway			
9	Pettifor [2] —Case 3		Stippling: none noted (examined)	Slightly underdeveloped nose	None	Normal exam	Normal	
10	Holmes [110]		Stippling: femoral trochanters and distal phalanges; cleft of posterior cervical vertebrae, short distal phalanges	Hypoplastic		Normal exam	Normal	
11	Pauli—A [95,98, 106]	+	Stippling: cervical and lumbar vertebrae, costal cartilage, trochanter, calcanei, femurs, patella; scoliosis	Severely hypoplastic with hypoplastic alae nasi, septation between alae nasi and columella	Respiratory distress and stridor as neonate, relieved by oral airway	Normal exam	Mild retardation	Hypotonic, hypertrophied clitoris, subluxable hips, peripheral pulmonic stenosis
12	O'Connor [115]		Stippling: none noted (examined)	Hypoplasia and deformity	Nasal stuffiness and needed frequent suctioning		Normal	
13	Johnson [112]		Stippling: spine, calcanei (spurring); frontal bossing, short phalanges, mild finger and toe deformity, increased density of axial skeleton	Hypoplastic base, choanal stenosis	Grunting and respiratory distress relieved by nosedrops	Normal exam	Normal	
14	Richman [96]		Stippling: calcanei	Hypoplastic bridge, small caliber nasal passages	Several dusky spells	Normal exam	Unknown	
15	MacLeod [113]		Stippling: region of epiphyses of greater trochanters	Small			Unknown	
16	Fourie [83]		Stippling: proximal femurs, vertebrae, sacrum, cuboids; calcified hyoid, short fingers, dystrophic nails	Hypoplastic and upturned, mild choanal stenosis		Normal exam	Unknown	
17	Pauli—C [117]		Stippling: vertebrae, calcanei, rib terminations; calcified hyoid, scoliosis and lordosis with hemivertebra at L-1, mild	Very small nose with septation between alae nasi and columella	Airway obstruction and CO_2 retention requiring intubation; persistent noisy breathing	Normal exam	Normal	Many desquamative skin rashes

Continued

Table II (Cont'd) Summary of Clinical Characteristics of 24 Cases of Warfarin Embryopathy

Case	References	Died	Skeletal	Nose	Breathing Problem	Eye	Development	Other
			brachydactyly and 5th toe clinodactyly					
18	Vanlaeys [104]		Stippling: calcanei, proximal humeri (irregularity)	Severe hypoplasia		Normal exam	Unknown	
19	Raivio [102] —Case 2	+	Stippling (seen prenatally): femoral heads, vertebrae, proximal and distal humeri, carpals and tarsals, pelvis, scapula; mild rhizomelia	Small, flattened with broad base, small nares	Severe CO_2 retention relieved by oral airway	Normal exam	(Died)	Bilateral simian creases, feeding problems; died of bronchopneumonia
20	Lutz [108]—Case 17		No information available	Soft, flat little nose			Unknown	
21	Robinson [107]		Stippling: vertebral transverse processes, heads of ribs and laryngeal cartilages	Hypoplasia of nasal cartilage	Severe respiratory distress as neonate relieved by oral airway	Normal exam	Normal	
22	Harrod [110] —Case 1		No neonatal films, normal at 3 yr 6 mo	Hypoplasia			Language delay, behavior problems	Sibling of our patient (Case 23)
23	Harrod [110] —Case 2		Stippling: cervical, thoracic and lumbar vertebrae, tarsal bones, distal phalanges; thoracic 'butterfly' vertebrae	Hypoplasia		Mesodermal dysgenesis of right eye	Normal	Mild low frequency hearing loss; sibling of our patient (Case 22)
24	Madden [114]		Stippling: sacrum, feet	Hypoplasia	Minimal neonatal airway problems	Normal exam	Normal	CAT scan normal

central nervous system injury was fetal hemorrhage, with scarring and secondary central nervous system abnormalities due to distorted growth [7]. **Table III** summarizes 13 cases in which intrauterine exposure to coumarin derivatives was followed by the birth of infants with recognized central nervous system abnormalities. We have eliminated those patients in whom the central nervous system problems appear to be related to late prenatal, perinatal or neonatal hemorrhage [13,24,33,35,40,58,64,94,100,108]. The cases are listed by the investigator or by the reporting medical professional. As in Tables I and II, estimation of exposure has been converted to gestational weeks in all cases. Five patients (CNS Cases 2,3,4,6 and 8) have signs of the embryopathy as well as central nervous system complications; all had exposure during the first trimester. Six have had structural studies that demonstrate anatomic abnormalities (CNS Cases 5,8,9,10,12 and 13). Although controversy about the validity of studies in certain cases exists (notably Case 12 [10]), certain patterns seem to be present. The first is dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation and mid-line cerebellar atrophy. In addition, two patients [7,76] had encephaloceles, which have been associated with Dandy-Walker malformation (135b). Another possible pattern is ventral mid-line dysplasia characterized by optic atrophy: eye anomalies are described in seven of the patients whose central nervous system was affected. However, no constant constellation of central nervous system abnormalities is apparent. Furthermore, there is no apparent correlation between time of exposure and the central nervous system effects demonstrable.

In contrast to the warfarin embryopathy, there does not seem to be a critical period of prenatal exposure to coumarin derivatives that is associated with central

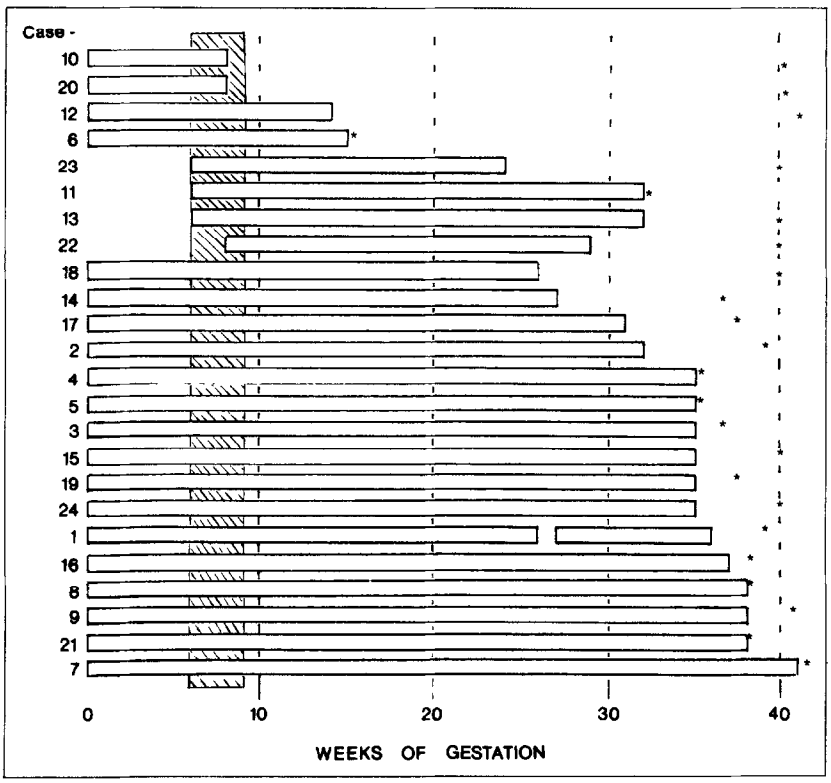

Figure 1. Exposure to coumarin derivatives by weeks of gestation in 24 cases of warfarin embryopathy. Cases are arranged by similar timing of exposure, with each bar representing exposure in an individual case. Asterisks indicate the time of birth in gestational weeks. For dosage of coumarin derivative, see Table I. Note that the critical period of exposure appears to be between six and nine weeks of gestation.

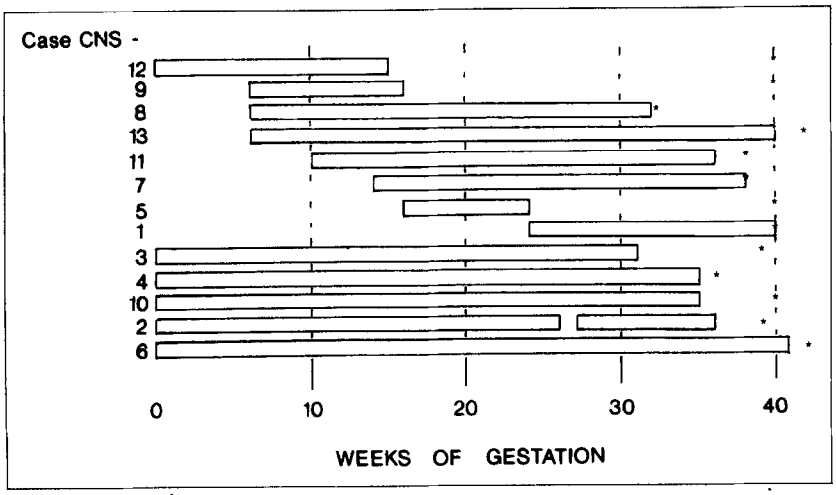

Figure 2. Exposure to coumarin derivatives by weeks of gestation in 13 cases of central nervous system abnormalities attributable to exposure to coumarin derivatives. Cases are arranged by similar timing of exposure, with each bar representing exposure in an individual case. Asterisks indicate the time of birth in gestational weeks. For dosage of coumarin derivatives see Table III. Note that there does not appear to be any critical period of exposure, although all patients were exposed in the second and/or third trimesters.

TABLE III **Summary of 13 Cases with Central Nervous System Abnormalities not Clearly Caused by Intrauterine or Perinatal Hemorrhage Whose Mothers Were Exposed to Coumarin Derivatives During Pregnancy**

CNS Case	Reference	Affected with Embryopathy ?	Brain Malformation	Structural Study of Brain	Eye Abnormalities	Development	Other	Died	Anticoagulant	Daily Dose (mg)	Exposure (wk of gestation)
1	Quenneville [31]	No	Microcephaly, cerebral agenesis		Optic atrophy	No follow-up available			Warfarin		24–40
2	DiSaia [1,45,73]	Yes			Bilateral optic atrophy, totally blind	Mild retardation			Warfarin		0–26, 28–36
3	Kerber [53,105]	Yes				Moderate-severe retardation	Seizures, spasticity, deafness	+	Warfarin	7.5	0–31
4	Tejani [76]	Yes	Occipital meningocele; hydrocephalus		Microphthalmia, probably blind	Severe retardation			Warfarin	5–10	0–35
5	Hall [109]	No	Cerebellar atrophy, cerebral atrophy, ventricular dilatation	CAT scan	Optic atrophy, decreased acuity on right	Moderate retardation	Spasticity, seizures		Warfarin	10–12.5	16–24
6	Pettifor [2,151]—Case 1	Yes			Right eye optic atrophy and blindness	Mild retardation			Phenindoine		0–41
7	Sherman [11]	No	Severe microcephaly		? Blind	Retardation	Hypotonia		Warfarin	7.5	14–38
8	Pauli—A [95,98,106]	Yes	Diffuse cerebral atrophy	CAT scan		Retardation	Hypotonia	+	Warfarin	7.5–10	6–32
9	Warkany [7]—Case 1	No	Hydrocephalus (blood in cranial cavity)	Postmortem		Died neonatally	Blood in cranial cavity at *postmortem* examination	+	Warfarin	5	6–16
10	Warkany [7]—Case 2	No	Parieto-occipital cephalocele, hydrocephalus, Dandy-Walker malformation	Angiography, ventriculography			Abnormal urinary tract		Warfarin	10	0–35
11	Carson [7]	No	Microcephaly		Blind	Retardation	Spasticity		Warfarin	4.5	10–36
12	Holzgreve [9]	No	Posterior fossa cyst, reported (questionable) agenesis of the corpus callosum and ventriculomegaly	CAT scan		Mild to moderate retardation	Hypotonia, seizures		Warfarin	10	0–15
13	Pauli—B [116]	No	Dandy-Walker malformation, possible agenesis of the corpus callosum	CAT scan		Borderline-mild retardation	Hypertonicity, mild spasticity, hyperreflexia, severe scoliosis, growth failure		Warfarin		6–40

nervous system abnormalities (**Figure 2**). All subjects were exposed to coumarin derivatives during the second and/or third trimester. The two patients with exposure in only the first and early second trimesters (CNS Cases 9 and 12) are also the two with the most equivocal findings.

Sequelae from central nervous system abnormalities have been more significant and debilitating than those of the embryopathy. None of the patients was completely normal on follow-up. Mental retardation, found in all, and blindness, found in half, result in significant personal and societal burden. In addition, spasticity was present in four (31 per cent), seizures in three (23 per cent), and deafness, scoliosis and growth failure in one each. Three died (23 per cent).

Incidence Data. The cases of coumarin derivative exposure during gestation, ascertained from a literature review (1945–1978), are catalogued in **Table IV.** We have endeavored to eliminate any repetition of cases reported multiple times. Over-all, a total of 418 cases was discovered. Although we attempted complete literature ascertainment, some cases may have been overlooked; however, such cases would probably not alter the data significantly.

Conditions for which anticoagulants were used most often included thrombophlebitis, embolic disease and valvular prostheses. Other indications were hypertension, preeclampsia, eclampsia, glomerulonephritis and antithrombin III deficiency. Various coumarin derivatives were used, with warfarin being the most frequently utilized. In many cases, multiple other drugs were taken during pregnancy.

In many instances, mothers who took coumarin derivatives were either switched to heparin near term or, in some cases, took heparin at some other time during the pregnancy. Since no specific fetal abnormalities have been associated with the use of heparin during pregnancy (as would be anticipated for a drug which does not cross the placenta [136]), all cases in which there was significant exposure to both classes of compounds are included in calculations of the coumarin derivative exposed group. Because of this arbitrary division, we cannot exclude possible effects of heparin-coumarin derivative interaction, nor can we estimate the increased risks of the complicated pregnancies themselves in which coumarin derivatives were usually used. In none of the cases listed under "heparin use during pregnancy" was ingestion of any oral anticoagulant reported. The many different doses and dosage schedules of coumarin derivatives and the incomplete reporting of prothrombin times do not allow analysis for these variables. In most series, tabulations of abnormalities and complications undoubtedly represent the lowest possible estimates since many examinations of newborns may have been incomplete, problems may not have been apparent in the neonatal period and, in most cases, follow-up information is not available.

In 38 per cent of the cases (156 of 418) the patients ingested coumarin derivatives during all three trimesters, usually continuing until just prior to delivery. In 75 per cent of these (118 of 156) the patients were reported to have had normal liveborn infants. Nearly one fourth of the patients had a variety of fetal complications including spontaneous abortion, stillbirth, prematurity, central nervous system abnormalities, embryopathy and fetal hemorrhage (**Table V**). Nine patients (about 2 per cent) had anomalies which are probably unrelated to the use of oral anticoagulants (**Table VI**). This low figure for congenital malformations probably reflects incomplete ascertainment of neonatal abnormalities, but it also indicates that exposure to coumarin derivatives carries with it no marked risk for malformations in general.

Isolated exposure to coumarin derivatives in the first trimester (45 cases) was associated with a high complication rate. Of the 31 patients (69 per cent) with difficulties, the vast majority had spontaneous abortions (22 cases). This probably represents, in part, an ascertainment bias, since those pregnancies in which abortion occurs would have no opportunity for exposure in subsequent trimesters. Exposure during the first plus the second trimester likewise resulted in a high incidence of abortions, stillbirths and embryonic changes (over-all complication rate of 67 per cent, 14 of 21). Isolated exposure during the second trimester, the third trimester

TABLE IV **Fetal and Neonatal Complications Associated with Exposure to Coumarin Derivatives During Various Trimesters**

Trimesters of Exposure	Outcome	No.	References
1st	Liveborn, no complications	14	[12,14,20,23,26,27,30,44,61,100,108]
	Liveborn with		
	Embryopathy	2	[89,108]
	Prematurity, normal	4	[20,54,100]
	Prematurity, died	1	[49]
	Other problems	2	[99,101]
	Spontaneous abortion	22	[2,51,72,75,94,100,108]
	Total	45	

Table IV (Cont'd) Fetal and Neonatal Complications Associated with Exposure to Coumarin Derivatives During Various Trimesters

Trimesters of Exposure	Outcome	No.	References
1st/2nd	Liveborn, no complications	7	[21,34,48,51,60,65,100]
	Liveborn with		
	Embryopathy	1	[104]
	Central Nervous System effects	2	[7,10]
	Spontaneous abortion	11	[40,72,91,108]
	Stillborn without reported hemorrhage	2	[67,91]
	Total	23	
1st/3rd	Liveborn, no complications	1	[81]
	Total	1	
2nd	Liveborn, no complications	16	[17,20,21,37,43,44,47,61,71,72,108]
	Liveborn with		
	Prematurity, normal	1	[30]
	Other problems	1	[42]
	Spontaneous abortions	2	[17,72]
	Stillborn without reported hemorrhage	3	[31,61,93]
	Total	23	
2nd/3rd	Liveborn, no complications	32	[16,17,21,30,38,40,44,61,63,72,77,82,87,91,108]
	Liveborn with		
	Central nervous system effects	2	[11,31]
	Prematurity, with hemorrhage	1	[40]
	Other problems	3	[17,80,94]
	Stillborn without reported hemorrhage	3	[17,25,26]
	Total	41	
3rd	Liveborn, no complications	67	[12,14,16–18,20–22, 28,30,40,41,43,44,61, 63,72,75,87,93]
	Liveborn with		
	Hemorrhage	4	[13,24,33,35]
	Prematurity, with hemorrhage	1	[20]
	Other problems	3	[17,72,108]
	Stillborn without reported hemorrhage	10	[28,29,31,39,43,61]
	Stillborn with hemorrhage	3	[15,24,31]
	Total	88	
All three	Liveborn, no complications	118	[2,16,21,32,36,44,46,50,51,55–57,59,61–63,67,69,70,72,74,77–81,84–86,88,91–93,97,100,101,103,108]
	Liveborn with		
	Hemorrhage	3	[64,72,94]
	Embryopathy	8	[1–3,83,96,102,107]
	Central nervous system effects	2	[7,9]
	Embryopathy and central nervous system effects	5	[2,45,53,76,95]
	Prematurity, normal	2	[65,91]
	Prematurity, died	3	[57,58,101]
	Prematurity, with hemorrhage	2	[58,100]
	Other problems	2	[80,91]
	Stillborn without reported hemorrhage	7	[52,58,61,91,94,108]
	Stillborn with hemorrhage	4	[58,100,108]
	Total	156	
Unclear	Liveborn, no complications	38	[19,31,66,68,101]
	Liveborn with		
	Prematurity, normal	1	[31]
	Other problems	1	[66]
	Spontaneous abortions	1	[31]
	Total	41	

TABLE V **Summary of Fetal and Neonatal Complications Associated with Exposure to Coumarin Derivatives**

Outcome	No.	
Liveborn, no complications		293
Liveborn, with problems		57
Hemorrhage	7	
Embryopathy	11	
Central nervous system effects	6	
Embryopathy and central nervous system effects	5	
Prematurity, normal	8	
Prematurity, died	4	
Prematurity, with hemorrhage	4	
Other problems	12	
Spontaneous abortion		36
Stillborn without reported hemorrhage		25
Stillborn with hemorrhage		7
Total		418

TABLE VII **Frequency of Positive Outcome Versus Time of Exposure to Coumarin Derivatives**

Time of Exposure	Live, No Complications	Other Outcome	Per Cent Positive Outcome
First trimester +/− second trimester	21	47	31
Nonfirst trimester (2nd, 2nd + 3rd, 3rd)	115	37	76
All trimesters	118	39	76
Total	254	123	67

and isolated exposure during the second plus third trimester all resulted in complication rates in the range of only 20 to 30 per cent (seven of 23, 21 of 88 and nine of 41, respectively) (see Table IV).

Table VII summarizes time of exposure versus risk of various complications. Although it appears that risk decreases when exposure to coumarin derivatives occurs later in pregnancy, this may in part reflect a correlation between the severity of maternal disease and the need for early initiation of anticoagulant therapy rather than being directly attributable to the effects of these compounds per se.

Comparison with Heparin. Since there are so few patients left untreated in whom anticoagulants would usually be considered indicated, the only comparison with coumarin derivative administration which seems feasible is with pregnant women treated with the alternative, heparin. We were able to find a total of 135 cases of heparin treatment (with no oral anticoagulants) during pregnancy. In many of these cases the patients were treated with heparin for relatively long periods, often using subcutaneous administration. The maternal complication rate may be higher when heparin is used. Of the 135 cases of heparin use, significant maternal hemorrhage was reported in 14 (10 per cent) (**Table VIII**), whereas three mothers died (2 per cent), two evidently secondary to treatment failure [40,72] and one secondary to hemorrhage [121] (Table VIII). In contrast, only four reports (1 per cent) of significant maternal hemorrhage [72,74] and two deaths (0.5 per cent) [42,94] associated with the use of coumarin derivatives were found in the literature. We have not been able to analyze whether this is related to different indications for the use of heparin or whether it truly reflects a serious maternal risk caused by heparin. Fetal death or morbidity from prematurity, stillbirth and hemorrhage was very frequent after exposure to heparin during gestation (**Table IX**). Particularly noteworthy is the complication rate secondary to isolated exposure in the first and/or second trimesters: of 11 pregnancies, nine infants were stillborn or were born prematurely and died. The over-all frequency of fetal or neonatal mortality or morbidity was 36 per cent. Of liveborns, 24 per cent were premature (including 10 who died (**Table X**).

COMMENTS

Risk of Coumarin Derivatives During Gestation. Although some women with phlebitis during pregnancy

TABLE VI **Incidental Congenital Malformations in Children with History of In Utero Coumarin Derivative Exposure**

Reference	Trimesters Exposed	Anomalies
Brambel ([17], Case 8)	2,3	Asplenia, two-chambered heart, agenesis of the pulmonary artery
Brambel ([17], Case 14)	3	Anencephaly, spina bifida, congenital absence of the clavicles
Aaro ([66], Case 1)	?	Congenital heart disease, died at 24 hours of age
Henderson ([72], Case 18)	3	Fetal distress, focal motor seizures
Casanegra ([80], Case 7)	2,3	Bilateral polydactyly
Ibarra-Perez ([91], Case 14)	1,2,3	Congenital corneal leukoma
Oakley ([94], Case 35)	2,3	Undefined multiple congenital anomalies
Cox [99]	1	Asplenia, congenital heart disease, incomplete rotation of the gut, short broad phalanges, hypoplastic nails
Lutz ([108], Case 20)	3	Single kidney, toe deformities, other anomalies, died at 2 hours of age

TABLE VIII Maternal Complications Associated with Heparin Administration During Various Trimesters

Trimesters of Exposure	Maternal Outcome: All Right	Maternal Outcome: Hemorrhage	Maternal Outcome: Death	References
1st	0	0	2	[40,72]
1st/2nd	1	0	0	[129]
2nd	7	1	0	[25,63,82,120,129, 130,134]
2nd/3rd	11	1	0	[100,124,125,129,132]
3rd	56	9	1	[22,23,25,30,40,63,72, 93,100,118–124, 126–129,131]
All three	9	1	0	[100,108,133]
Unclear	34	3	0	[66,68,119,124,129]
Total	118	15	3	

TABLE X Summary of Fetal and Neonatal Complications Associated with Exposure to Heparin

Outcome		No.
Liveborn, no complications		86
Liveborn, with problems		30
Hemorrhage	0	
Prematurity, normal	19	
Prematurity, died	10	
Prematurity, with hemorrhage	0	
Other problems	1	
Spontaneous abortions		2
Stillborn without reported hemorrhage		17
Stillborn with hemorrhage		0
Total		135

TABLE IX Fetal and Neonatal Complications Associated with Exposure to Heparin During Various Trimesters

Trimesters of Exposure	Outcome		No.	References
1st	Spontaneous abortion		2	[40,72]
		Total	2	
1st/2nd	Stillborn without reported hemorrhage		1	[129]
		Total	1	
2nd	Liveborn, no complications		2	[125,63]
	Liveborn with			
	Prematurity, died		2	[128,134]
	Stillborn without reported hemorrhage		4	[120,129,130]
		Total	8	
2nd/3rd	Liveborn, no complications		8	[100,124,125,129,132]
	Liveborn with			
	Prematurity, normal		1	[100]
	Other problems		1	[100]
	Stillborn without reported hemorrhage		1	[100]
		Total	11	
3rd	Liveborn, no complications		32	[22,23,30,40,63,72,100,119,120,122–124, 127–129,131]
	Liveborn with			
	Prematurity, normal		16	[63,93,118,120,126,129]
	Prematurity, died		7	[100,120,121,124,127,129]
	Stillborn without reported hemorrhage		11	[25,93,119,127,129]
		Total	66	
All three	Liveborn, no complications		7	[133]
	Liveborn with			
	Prematurity, normal		2	[100]
	Prematurity, died		1	[94]
		Total	10	
Unclear	Liveborn, no complications		37	[66,68,119,124,129]
		Total	37	

may not require anticoagulation, pregnancies complicated by severe thrombophlebitis, pulmonary emboli or prosthetic heart valves have catastrophic outcomes if anticoagulation is not employed [23,31,38,43]. Hemorrhagic risk of such anticoagulation has been recognized for over 30 years [13,31,39,43,58,137]. A variety of protocols have been devised in an effort to minimize this risk to both mother and fetus [16,20,21,28,31, 41,56,57,63,138].* However, with the recognition of the teratogenic potential of coumarin derivatives, therapeutic choices have become more difficult. Our literature review is an attempt to provide *estimates* of risk so that a more rational approach to the needed anticoagulation can be taken.

Accumulating cases from the literature is obviously less satisfactory than a controlled study; a well controlled study, however, has not and most likely will not be forthcoming since use of coumarin derivatives during pregnancy is now contraindicated by the manufacturers. In most reported cases neonatal examinations were cursory, and few neonates were followed or reexamined, so that subtle physical anomalies may have been overlooked and many central nervous system effects may have gone totally unrecognized. Those neonates with recognized embryopathic and/or central nervous system abnormalities are probably the most severely affected of a continuum of effects of coumarin-derivative therapy during gestation. Therefore, absolute risk figures cannot be well estimated. Nevertheless, some estimate needs to be made because of the absolute need for anticoagulation in some pregnant women or women who contemplate becoming pregnant.

Of greatest consequence, in terms of ultimate burden, are liveborn but abnormal infants. In 418 reported pregnancies with coumarin derivative exposure, a total of 57 liveborn infants with significant problems were reported (Table V). This figure does not include the unpublished cases of embryopathic or central nervous system effects known to us and reported here. Thus, of all published reports of pregnancies (including abortions and stillbirths) in which coumarin derivatives were used, 13 per cent of the pregnancies resulted in liveborn infants with significant problems; of all liveborn infants, 16 per cent were abnormal. Complications included hemorrhage, embryopathic effects, central nervous system abnormalities and prematurity. A total of 11 liveborn infants had primarily hemorrhagic manifestations, 16 had findings consistent with warfarin embryopathy, whereas 11 had significant central nervous system abnormalities (of which five also had embryopathic changes). Therefore, the best available estimate is that if coumarin derivatives are used during pregnancy, one sixth of the pregnancies will result in an abnormal liveborn infant, one-sixth will result in abortion or stillbirth and, at most, two-thirds will have an apparently normal outcome. Of significantly affected liveborn infants, those with hemorrhage or central nervous system abnormalities generally do poorly, whereas one half of those with embryopathy do well. Particularly impressive is the complication risk when coumarin derivatives are used in the first trimester alone: only about one third of these pregnancies resulted in normal, liveborn babies.

Warfarin Embryopathy. About one third of liveborn morbidity (and 16 of 418 cases over-all, or 4 per cent) following exposure to coumarin derivatives in utero is due to warfarin embryopathy (Tables I and II). Our case review demonstrates that exposure has occurred between the sixth and ninth weeks of gestation in all patients who show signs of embryopathy. The mechanism for production of the warfarin embryopathy is not completely understood. Initially, it was proposed that the abnormalities in warfarin embryopathy, particularly the stippled calcifications and nasal cartilage hypoplasia, might be secondary to fetal microhemorrhage and subsequent calcification of the hemorrhagic regions [1]. The demonstration that all embryopathic manifestations occurred when mothers took coumarin derivatives between six and nine weeks of gestation makes this hypothesis unlikely since clotting factors affected by vitamin K antagonists are not yet demonstrable in the embryo at the six to nine weeks stage of development [139].

A molecular mechanism similar to the effect of coumarin derivatives on vitamin K-dependent clotting factors may, however, be operative. Coumarin derivatives exert their anticoagulant effect by inhibiting post-translational carboxylation of coagulation proteins [140]. Vitamin K is also directly involved in the post-translational modification of many other proteins by formation of gamma-carboxyglutamyl residues from glutamyl residues. This type of modification is necessary for many proteins to be able to bind calcium [140]. Calcium-binding, vitamin K-dependent and coumarin derivative-inhibitable gamma carboxyglutamate-containing proteins have been isolated from bone [141–144]. The so-called 'osteocalcins' [143] have biochemical activity that may reflect their role in the control of calcification during embryonic development [143]. Inhibition of such proteins by coumarin derivatives during a critical embryologic period of ossification could explain many of the features of warfarin embryopathy, including nasal hypoplasia, stippled calcification, extremity shortening and vertebral abnormalities (see **Figure 3**).

* It is generally recognized that perinatal and neonatal hemorrhage contraindicate the use of coumarin derivatives in the last portion of the third trimester. The generally standard practice had been to establish anticoagulation with heparin and then to use coumarin derivatives, such as warfarin, so as to maintain a prothrombin time of slightly less than two times normal (usually requiring about 5 to 10 mg/day of warfarin). The warfarin was then again replaced with heparin in the terminal part of the pregnancy, with short temporary reversal with protamine sulfate often employed at delivery.

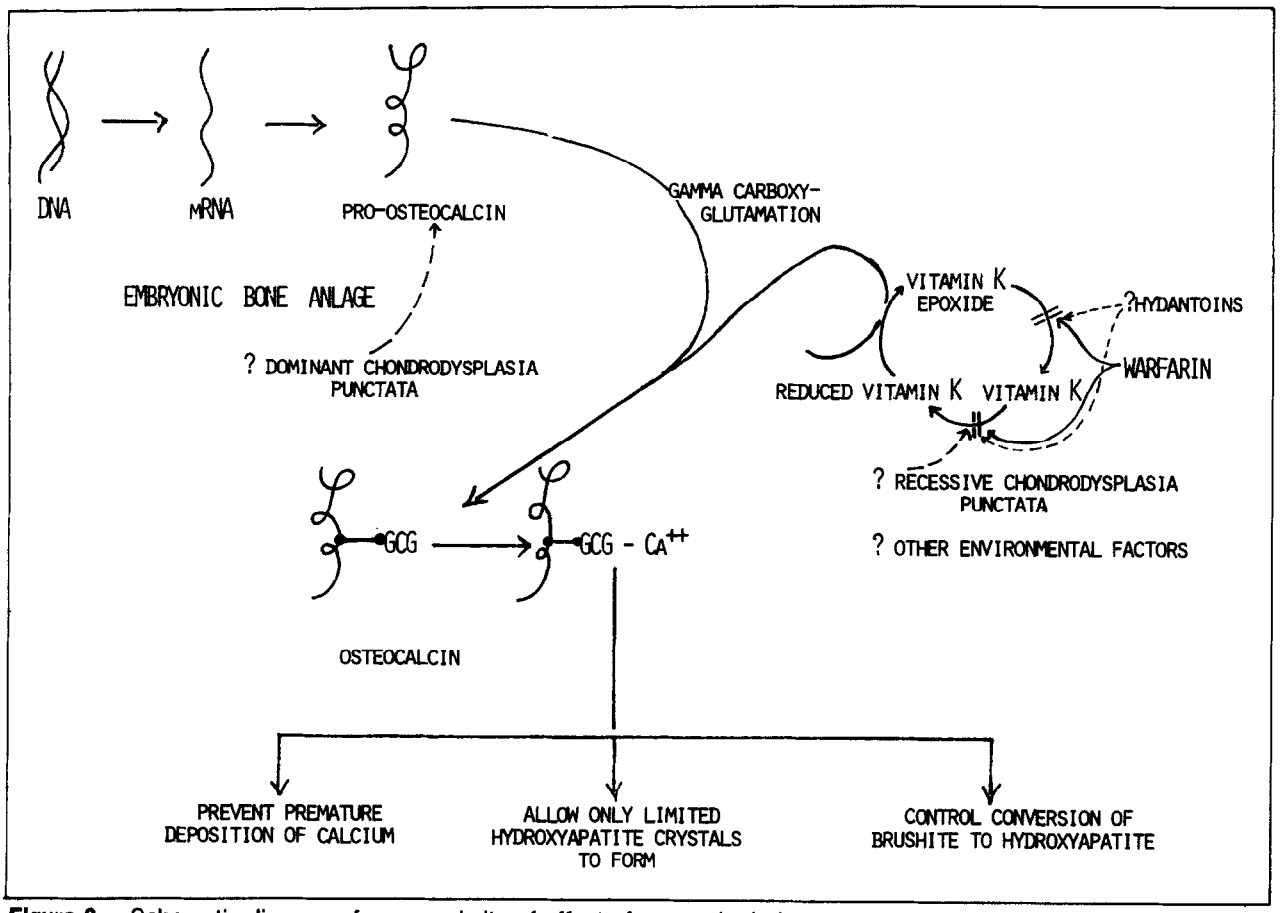

Figure 3. Schematic diagram of proposed site of effect of coumarin derivatives in causing abnormal embryonic calcium deposition and subsequent bone formation and growth. Specific sites of effects of hydantoins, and the dominant and recessive forms of chondrodysplasia punctata are also postulated. GCG = gamma-carboxyglutamate.

Warfarin embryopathy can be considered a phenocopy of chondrodysplasia punctata. Chondrodysplasia punctata is, in fact, a group of diseases characterized primarily by stippled epiphyses. Spranger et al. [145] delineated various types with various modes of inheritance, to which should probably be added the X-linked variant of Curry [146] and the sporadic form described by Sheffield et al. [147]. Of the various types, Sheffield's cases most closely resemble warfarin embryopathy clinically. The various forms of chondrodysplasia punctata might also be related to defects in the osteocalcin system. For example, recessive forms might reflect enzymatic deficiencies in the gamma-carboxylation process whereas dominant forms could be due to structural defects in the protein to be carboxylated (see Figure 3).

A similar molecular mechanism may account for the fetal hydantoin syndrome. The fetal hydantoin syndrome [148] shares some characteristics with warfarin embryopathy (growth retardation, nasal hypoplasia, distal extremity hypoplasia and variable central nervous system involvement). Sheffield et al. [147] described two patients with mild chondrodysplasia punctata who had been exposed to diphenylhydantoin in utero; one of the original cases of warfarin embryopathy [149–151] was in a mother who had also ingested diphenylhydantoin and primadone throughout pregnancy. Since diphenylhydantoin can cause fatal neonatal hemorrhage when taken shortly before delivery [152,153], secondary to defects in vitamin K-dependent coagulation factors [152,154], it may interfere with the gamma carboxylation of both coagulation factors and other calcium-binding proteins, including osteocalcin. Roentgenographic screening of neonates with exposure to diphenylhydantoin might demonstrate a high incidence of stippling. If this hypothesis is true, the effects of hydantoin exposure in the fetus and the risk of heritable chondrodysplasia punctata *might* be partially or wholly abrogated by the administration of vitamin K during gestation.

The proposed mechanisms are summarized in Figure 3.

Central Nervous System Abnormalities. A small proportion of liveborn infants (11 in 418 published cases, or 3 per cent) exposed to coumarin derivatives during pregnancy demonstrate central nervous system abnormalities. The central nervous system effects have been

TABLE XI Summary of Fetal and Neonatal Outcome After Anticoagulant Use in Pregnancy

	Per Cent of Pregnancies	
	Coumarins	Heparin
Liveborn		
Subsequent infant death	2.4	7.4
Persistent sequelae	10.4	0.7
Premature, otherwise 'normal'	1.9	14.1
Spontaneous abortions	8.6	1.5
Stillbirths	7.7	12.6

heterogeneous, as described in Table III. Five of 13 subjects with central nervous system abnormalities also demonstrated findings consistent with warfarin embryopathy. This does not imply, however, that the brain abnormalities are really part of the embryopathy or were produced by the same mechanism. Those patients with both manifestations were exposed to coumarin derivatives for extended periods during gestation. Long exposure and the lack of a critical period for central nervous system and eye abnormalities support the contention that an independent and perhaps nonspecific mechanism accounts for the central nervous system effects. This supports Warkany's hypothesis [7] that the central nervous system effects could be *de*formations which may occur at any time following organogenesis as a result of dysharmonic growth (secondary, for example, to earlier fetal hemorrhage and subsequent scarring) rather than *mal*formations arising during the period of organogenesis. Thus, exposure to coumarin derivatives during weeks six to nine of gestation results in the risk of warfarin embryopathy developing in the baby, whereas exposure in the second and third trimesters appears to independently predispose to the development of central nervous system anomalies.

Comparative Risk of Heparin. Heparin has been proposed as an alternative to coumarin derivative therapy [124,155]. Methods are available for its administration on an outpatient basis [124,155,156]. It has been used over extended periods with maintenance of effective coagulation [124,155,156] although not without deleterious effect [157] (including hemorrhage [124, 158]; anaphylaxis [159]; osteoporosis [160,161]; neurologic complications [162]; painful nodules [159]; focal necrosis [159]; alopecia [163]; and significant technical difficulties in administration). Because it does not cross the placenta [136] it offers a theoretic advantage over warfarin for use during pregnancy.

Our data from 135 published cases of the use of heparin during pregnancy indicates a marked maternal complication rate. This includes hemorrhage in 14 of 135 mothers (10 per cent) and death in three (2 per cent). Whether this greater maternal complication rate is directly related to indications for the use of heparin alone, or whether it truly reflects a prohibitive maternal risk in the use of heparin, is unclear.

Excluding maternal morbidity and mortality, pregnancy outcome is still little better than with the use of coumarin derivatives. Thirty-three per cent of pregnancies resulted in stillbirth (17 cases) or prematurity (29 cases). Over-all, we estimate that if heparin is used during pregnancy, one-eighth of the pregnancies will end in stillbirth, one-fifth will be premature and, at most, two-thirds will have a normal outcome (see Table X).

Table XI provides an overview comparison of the outcome in pregnancies in which coumarin derivatives or heparin are used. Whereas heparin administration in pregnancy resulted in perinatal (13 per cent) or neonatal (7 per cent) death in 20 per cent of the reported cases, exposure to coumarin derivatives was more often associated with earlier fetal loss (9 per cent spontaneous abortions) or liveborn infants with persistent sequelae (10 per cent, of which 4 per cent was due to warfarin embryopathy and 3 per cent to central nervous system effects).

Data relating trimesters of exposure to heparin and outcome are too fragmentary to have any real meaning. It is unknown whether the use of heparin carries decreased risk at particular times during gestation. Lack of follow-up information prevents evaluation of infant growth and development.

No animal or human studies of possible mechanisms of heparin's deleterious effect on the fetus have been made (despite its continued use in pregnant women requiring anticoagulation). Since it does not cross the placenta [136], its effects might derive from its chelating capacity, which might indirectly result in calcium (or other cation) deficiency in the embryo and fetus subsequent to maternal depletion.

Although the ultimate burden of the abnormal outcomes of pregnancy after the use of heparin may be less, the addition of apparently increased maternal morbidity and mortality make a choice between these alternative modalities very difficult.

Recommendations. Both heparin and coumarin derivatives, when administered during pregnancy, carry substantial risks both to the mother and the fetus. Given the inherent risks of pregnancies complicated by the indications for anticoagulation (embolic phenomena, prosthetic heart valves, etc.), the most prudent and advisable course of action is preconceptual counselling and, in most cases, prevention of pregnancy. Should a woman become pregnant, or should medical indications for anticoagulation arise during pregnancy, intervention in the form of a therapeutic abortion should be offered. Prenatal diagnosis by roentgenologic evaluation may be possible and, in fact, we have monitored three cases in this way. The over-all likelihood of a relatively normal outcome (from published cases) of a pregnancy in which *either* coumarin derivatives or heparin is used is approximately two-thirds. We are aware of many other cases of exposure to coumarin derivatives in which the outcome was normal. Therefore, although we

earlier recommended heparin as an alternative mode of therapy [6], this review suggests that heparin is *not* a clearly superior alternative method of anticoagulation during pregnancy; because of difficulties in administering heparin, coumarin derivatives remain a reasonable alternative for anticoagulant therapy in pregnancy if the relative risks are explained to the parents.

Perhaps, as more precise knowledge of the mechanism of the teratogenic effects of coumarin derivatives is accumulated, means of abrogating these effects will be found.

ADDENDUM

We are now aware of five additional patients with embryopathic abnormalities associated with exposure to coumarin derivatives in utero.

We inadvertently overlooked the report of Abbott et al. [164] which describes an infant exposed to a coumarin derivative from 0 to 24 weeks of gestation, and delivered at 29 weeks. He had nasal hypoplasia and "stippling of all epiphyses," as well as laryngeal calcification. The latter may have contributed to his death at 21 days of age.

Smith and Cameron [165] briefly described a 33 to 35 weeks gestation infant exposed throughout pregnancy to warfarin, who had nasal hypoplasia and bilateral subdural hematomas. The infant died at 3 hours of age. No roentgenographic findings or other details were reported.

Guillot et al. [166] reported on a premature male infant with nasal hypoplasia and calcaneal stippling whose mother took a coumarin derivative during the first 28 weeks of pregnancy. The infant was born at 30 weeks gestation, weighed 1,200 g and was 38 cm long. In addition to the findings consistent with warfarin embryopathy, the infant was microcephalic; at two months of age he was hypotonic and developmentally delayed.

Stevenson et al. [167] describe an infant born at 31 weeks gestation after exposure to warfarin throughout pregnancy. The 1,000 g female had typical nasal hypoplasia with small air passages which contributed, in part, to her neonatal respiratory distress. Stippling was present at the vertebrae, femurs and tarsal bones. Follow-up demonstrated growth failure, developmental retardation and bilateral optic atrophy. The patients of Guillot et al. [166] and Stevenson et al. [167] both appear to be additional examples of persons with both embryopathic and central nervous system effects secondary to exposure to coumarin derivatives.

One of us (R.M.P.) has recently examined an 1,820 g, 38 weeks gestation female infant with minimal features of warfarin embryopathy. Her mother was treated with warfarin from the third to the 16th week of gestation because of maternal concentric ventricular hypertrophy, aborted sudden death and arrhythmias. The infant was severely undergrown, had a depressed nasal bridge, hypoplastic nose and relatively small alae nasi. Roentgenograms demonstrated only an area of asymmetry and questionable stippling to the right of the sacrum. This infant illustrates minimal involvement in an at-risk infant which could go unrecognized without careful examination.

These five patients increase the number of cases of warfarin embryopathy known to us to 29.

ACKNOWLEDGMENT

We thank the following persons for information utilized in the course of writing this paper: Mason Barr Jr., M.D., Melvin Becker, M.D., Werner A. Bleyer, M.D., Alphonse R. Burdi, Ph.D., M. Michael Cohen Jr., D.D.S., Bryan D. Hall, M.D., Mary Jo Harrod, Ph.D., Dale Heisinger, M.D., Lewis B. Holmes, M.D., J. Fred Johnson, M.D., David A. Luthy, M.D., Dennis J. Lutz, M.D., Patrick M. MacLeod, M.D., John D. Madden, M.D., Elizabeth Newkom, M.D. of Endo Laboratories, Nancy O'Connor, R.N., M.S.W., Andrew K. Poznanski, M.D., Edward M. Richman, M.D., Leslie J. Sheffield, M.R.A.C.P., D.C.H., Manuel E. Soto-Viera, M.D., Jurgen Spranger, M.D., Arthur R. Thompson, M.D., Josef Warkany, M.D., Robert S. Wilroy Jr., M.D., and Irving S. Wright, M.D. We also acknowledge the help of Julia Kant, Ute Ochs, M.D., and Virginia P. Sybert, M.D., in translating certain foreign language articles.

REFERENCES

1. Becker MH, Genieser NB, Finegold M, et al.: Chondrodysplasia punctata. Is maternal warfarin a factor? Am J Dis Child 129: 356, 1975.
2. Pettifor JM, Benson R: Congenital malformations associated with the administration of oral anticoagulants during pregnancy. J Pediatr 86: 459, 1975.
3. Shaul WL, Emery H, Hall JG: Chondrodysplasia punctata and maternal warfarin use during pregnancy. Am J Dis Child 129: 360, 1975.
4. Hall JG: Embryopathy associated with oral anticoagulant therapy. Birth Defects 12: 33, 1965.
5. Warkany J: A warfarin embryopathy? Am J Dis Child 129: 287, 1975.
6. Shaul WL, Hall JG: Multiple congenital anomalies associated with oral anticoagulants. Am J Obstet Gynecol 127: 191, 1977.
7. Warkany J, Bofinger M: Le role de la coumadine dans les malformations congenitales. Med Hyg 33: 1454, 1975.
8. Warkany J: Warfarin embryopathy. Teratology 14: 205, 1976.
9. Carson M, Reid M: Warfarin and fetal abnormality. Lancet 1: 1127, 1976.
10. Holzgreve W, Carey JC, Hall BD: Warfarin-induced fetal abnormalities. Lancet 2: 914, 1976.
11. Sherman S, Hall BD: Warfarin and fetal abnormality. Lancet 1: 692, 1976.
12. Yahr MD, Reich C, Eggers C: The treatment of thrombophlebitis. Surg Gynecol Obstet 80: 615, 1945.
13. von Sydow G: Hypoprotrombinemi och hjärnskada hos barn till dikumarin-behandlad moder. Nord Med 34: 1171, 1947.

14. Felder DA: Evaluation of the various clinical signs of thrombophlebitis and experience in therapy with anticoagulants. Surg Gynecol Obstet 88: 337, 1949.
15. Sachs JJ, Labate JS: Dicumarol in the treatment of antenatal thromboembolic disease. Am J Obstet Gynecol 57: 965, 1949.
16. Adamson DL, Weaver RT, Jaimet CH: A new view on the use of dicumarol in the pregnant patient. Am J Obstet Gynecol 59: 498, 1950.
17. Brambel CE, Fitzpatrick VdeP, Hunter RE: Protracted anticoagulant therapy during the antenatal period. Trans N Engl Obstet Gynecol Soc 5: 27, 1951.
18. Davis WL: Antepartum phlebothrombosis and thrombophlebitis. Am J Obset Gynecol 62: 353, 1951.
19. Thornton WN (quoted in Davis [18]): Antepartum phlebothrombosis and thrombophlebitis. Am J Obstet Gynecol 62: 353, 1951.
20. Wright HP: Venous thrombosis during pregnancy treated with dicoumarin. J Obstet Gynecol Br Emp 59: 272, 1951.
21. Mansell RV: Antepartum dicumarol therapy. Am J Obstet Gynecol 64: 155, 1952.
22. Flood CM: Antepartum femoral thrombosis. J Obstet Gynecol Br Emp 60: 706, 1953.
23. Ullery JC: Thromboembolic disease complicating pregnancy and the puerperium. Am J Obstet Gynecol 68: 1243, 1954.
24. Gordon RR, Dean T: Foetal deaths from antenatal anticoagulant therapy. Br Med J 2: 719, 1955.
25. Blum M, Barre W: Anticoagulant treatment of phlebothrombosis during pregnancy. Am J Obstet Gynecol 73: 440, 1957.
26. Forssell J, Brunila T: Cardiac infarction and pregnancy. Acta Med Scand 157: 387, 1957.
27. Lloyd TS: Dicumarol in antepartum thrombophlebitis. A case report. Va Med 84: 560, 1957.
28. Parker RT, Anlyan WG, Mairs DA, et al.: Thromboembolic complications of pregnancy. South Med J 50: 1228, 1957.
29. Epstein WA: Antepartum fetal death during anticoagulant therapy for thromboembolism. J Mt Sinai Hosp NY 26: 562, 1959.
30. McElin TW, Danforth DN, Buckingham JC: Thrombophlebitis in antepartum patients. Q Bull Northwestern Univ Med Sch 33: 242, 1959.
31. Quenneville G, Barton B, McDevitt E, et al.: The use of anticoagulants for thrombophlebitis during pregnancy. Am J Obstet Gynecol 77: 1135, 1959.
32. Feldman R, Smith L: Antepartum thrombophlebitis treated by long-term use of bishydroxycoumarin. Am J Obstet Gynecol 79: 810, 1960.
33. Pagliari M: Sui possibili effetti nocivi sulla madre e il feto dei preparati dicumarolici usati in gravidanza. Quad Clin Ostet Ginec 15: 910, 1960.
34. Gopelrud CP, Anderson GS: Antepartum venous thrombosis with multiple pulmonary emboli: a case report and a discussion. J Iowa Med Soc 51: 771, 1961.
35. Joseph R, Ribierre M, Hemery O, et al.: Les hémorragies foetales provoquées par l'administration d'anticoagulants a la femme enceinte. Ann Pediatr 37: 359, 1961.
36. Krembs MA, Kozina TJ: Antenatal pulmonary embolic disease. Am J Obstet Gynecol 81: 1233, 1961.
37. Naden RS, Johnson HF, Murray EN: Myocardial infarction during pregnancy. JAMA 178: 659, 1961.
38. Finnerty JJ, MacKay BR: Antepartum thrombophlebitis and pulmonary embolism. Report of a case and review of the literature. Obstet Gynecol 19: 405, 1962.
39. Mahairas GH, Weingold AB: Fetal hazard with anticoagulant therapy. Am J Obstet Gynecol 85: 234, 1963.
40. Cegelski FC, DeWeese JA, Lund CJ: Deep iliofemoral venous thrombosis during pregnancy. Am J Obstet Gynecol 89: 510, 1964.
41. Jennings JA, Hodgkinson CP: Anticoagulation for pulmonary embolism in pregnancy. Obstet Gynecol 24: 85, 1964.
42. DeVita VT, Wiener L, Massumi R: Antepartum thrombophlebitis and pulmonary embolization. Report of a case and review of the literature. Med Ann DC 34: 177, 1965.
43. Villasanta U: Thromboembolic disease in pregnancy. Am J Obstet Gynecol 93: 142, 1965.
44. Aaro LA, Johnson TR, Juergens JL: Acute deep venous thrombosis associated with pregnancy. Obstet Gynecol 28: 553, 1966.
45. DiSaia PJ: Pregnancy and delivery of a patient with a Starr-Edwards mitral valve prosthesis. Report of a case. Obstet Gynecol 28: 469, 1966.
46. Johnson AS, Meyers MP, Eckhous AS, et al.: Successful pregnancies in patients with prosthetic mitral valves. Mich Med 65: 718, 1966.
47. Husni EA, Pena LI, Lenhert AE: Thrombophlebitis in pregnancy. Am J Obstet Gynecol 97: 901, 1967.
48. Harthorne JW, Buckley MJ, Grover JW, et al.: Valve replacement during pregnancy. Ann Intern Med 67: 1032, 1967.
49. Bennett GG, Oakley CM: Pregnancy in a patient with a mitral-valve prosthesis. Lancet 1: 616, 1968.
50. Carty AT, Crowdes RL: Pregnancy in a patient with a mitral-valve prosthesis. Lancet 2: 456, 1968.
51. Hedstrand H, Cullhed I: Pregnancy after aortic-valve prosthesis. Lancet 2: 916, 1968.
52. Kenmure ACF: Pregnancy in a patient with a prosthetic mitral valve. J Obstet Gynaecol Br Commonw 75: 581, 1968.
53. Kerber IJ, Warr OS, Richardson C: Pregnancy in a patient with a prosthetic mitral valve. JAMA 203: 223, 1968.
54. Otterson WN, McGranahan G, Freeman MVR: Successful pregnancy with McGovern aortic prosthesis and long-term heparin therapy. Obstet Gynecol 31: 273, 1968.
55. Turner RWD, Kitchin AH: Pregnancy after mitral-valve prosthesis. Lancet 1: 862, 1968.
56. Bloomfield DK, Rubinstein LI: Mitral-valve prosthesis, warfarin anticoagulation, and pregnancy. Lancet 2: 290, 1969.
57. Olwin JH, Koppel JL: Anticoagulant therapy during pregnancy. A new approach. Obstet Gynecol 34: 847, 1969.
58. Palacios-Macedo X, Diaz-Devis C, Escudero J: Fetal risk with the use of coumarin anticoagulant agents in pregnant patients with intracardiac ball valve prosthesis. Am J Cardiol 24: 853, 1969.
59. Szekely P, Snáith L: Mitral-valve prosthesis, warfarin anticoagulation, and pregnancy. Lancet 2: 598, 1969.
60. Bemiller CR, Forker AD, Morgan JR: Complete heart block, prosthetic aortic valve, and successful pregnancy. JAMA 214: 915, 1970.
61. Fillmore SJ, McDevitt E: Effects of coumarin compounds on the fetus. Ann Intern Med 73: 731, 1970.
62. Friefeld DM: Successful outcome of pulmonary embolism in the first trimester of pregnancy. J La State Med Soc 122: 177, 1970.
63. Hirsh J, Cade JF, O'Sullivan EF: Clinical experience with anticoagulant therapy during pregnancy. Br Med J 1: 270, 1970.
64. Ikonen E, Merikallio E, Osterlund K, et al.: Mitral-valve prosthesis, warfarin anticoagulation, and pregnancy. Lancet 2: 1252, 1970.
65. Laros RK, Hage ML, Hayashi RH: Pregnancy and heart valve prostheses. Obstet Gynecol 35: 241, 1970.
66. Aaro LA, Juergens JL: Thrombophlebitis associated with pregnancy. Am J Obstet Gynecol 109: 1128, 1971.
67. Buxbaum A, Aygen MM, Shahin W, et al.: Pregnancy in patients with prosthetic heart valves. Chest 59: 639, 1971.
68. Duncan ID, Coyle MG, Walker J: Management and treatment of 34 cases of antepartum thromboembolism. J Obstet Gynecol 78: 904, 1971.
69. Jenkins BS, Braimbridge MV: Management of anticoagulant therapy during pregnancy in patients with prosthetic heart valves. Thorax 26: 206, 1971.
70. Reid JM, Barclay RS: Pregnancy and mitral valve prosthesis. Br Med J 1: 326, 1971.

71. DeJager NST, Boyd NF, Ginsburg AD: Attempted abortion by the use of bishydroxycoumarin. Can Med Assoc J 107: 50, 1972.
72. Henderson SR, Lund CJ, Creasman WT: Antepartum pulmonary embolism. Am J Obstet Gynecol 112: 476, 1972.
73. Holmes LB, Moser HW, Halldórsson S, et al.: Mental retardation. An Atlas of Diseases with Associated Physical Abnormalities, New York, Macmillan Co, 1972. p 136.
74. Ibarra-Pérez C, Bosque-Ruiz M: Pregnancy in 6 patients with Starr-Edwards heart valve prostheses. Am J Cardiol 30: 565, 1972.
75. Kanarek KS, Bloom KR: Successful pregnancy after aortic and mitral valve replacements. S Afr Med J 47: 1373, 1973.
76. Tejani N: Anticoagulant therapy with cardiac valve prosthesis during pregnancy. Obstet Gynecol 42: 785, 1973.
77. Buyse FGC, Wormgoor BH, Bernard JTh, et al.: Anticoagulant therapy of patients with repeated placental infarction. Obstet Gynecol 43: 844, 1974.
78. Salas G, Walls W, Bianchi R: Manejo de una embarazada con reemplazo valvular y tratamiento anticoagulante. Rev Chil Obstet Ginecol 39: 93, 1974.
79. Biale Y, Lewenthal H, Gueron M, et al.: Cesarean section in a patient with a mitral valve prosthesis. Isr J Med Sci 11: 906, 1975.
80. Casanegra P, Aviles G, Maturana G, et al.: Cardiovascular management of pregnant women with a heart valve prosthesis. Am J Cardiol 36: 802, 1975.
81. Cokkinos D, Papadakis N, Kaskarellis D, et al.: Pregnancy and successful delivery in a patient with a Björk-Shiley aortic prosthesis. Acta Cardiol 28: 441, 1975.
82. Darbois PY: Attitude de l'obstetricien face aux phlebites profondes gravidiques. Phlebologie 28: 131, 1975.
83. Fourie DT, Hay IT: Warfarin as a possible teratogen. S Afr Med J 49: 2081, 1975.
84. Holswade GR, Anditi L: Pregnancy in women with prosthetic heart valves. NY State J Med 75: 2374, 1975.
85. Moore DS, Trelford JD: Scoliosis and pregnancy. JAMA 233: 183, 1975.
86. Pridmore BR, Murray KH, McAllen PM: The management of anticoagulant therapy during and after pregnancy. Br J Obstet Gynecol 82: 740, 1975.
87. Ramsay DM: Thromboembolism in pregnancy. Obstet Gynecol 45: 129, 1975.
88. Ahmad R, Rajah SM, Mearns AJ, et al.: Dipyridamole in successful management of pregnant woman with prosthetic heart valve. Lancet 2: 1414, 1976.
89. Barr M, Burdi AR: Warfarin-associated embryopathy in a 17-week-old abortus. Teratology 14: 129, 1976.
90. Ibarra-Pérez C, Alvarez de la Cadena O, Portillo-Pérez S, et al.: Embarazo en pacientes con dos protesis cardiacas y drogas antitromboticas. Ginecol Obstet Mex 40: 53, 1976.
91. Ibarra-Pérez C, Arevalo-Toledo N, Alvarez de la Cadena O, et al.: The course of pregnancy in patients with artificial heart valves. Am J Med 61: 504, 1976.
92. McCans JL, Wenger NK: Problems in management of the pregnant patient with rheumatic heart disease and valve prosthesis. South Med J 69: 1007, 1976.
93. Merrill LK, VerBurg DJ: The choice of long-term anticoagulants for the pregnant patient. Obstet Gynecol 47: 711, 1976.
94. Oakley C, Doherty P: Pregnancy in patients after valve replacement. Br Heart J 38: 1140, 1976.
95. Pauli RM, Madden JD, Kranzler KJ, et al.: Warfarin therapy initiated during pregnancy and phenotypic chondrodysplasia punctata. J Pediatr 88: 506, 1976.
96. Richman EM, Lahman JE: Fetal anomalies associated with warfarin therapy initiated shortly prior to conception. J Pediatr 88: 509, 1976.
97. Zucker ML, Gomperts ED, Marcus RG: Prophylactic and therapeutic use of anticoagulants in inherited antithrombin III deficiency. S Afr Med J 50: 1743, 1976.
98. Collins P, Olufs R, Kravitz H, et al.: Relationship of maternal warfarin therapy in pregnancy to chondrodysplasia punctata: report of a case. Am J Obstet Gynecol 127: 444, 1977.
99. Cox DR, Martin L, Hall BD: Asplenia syndrome after fetal exposure to warfarin. Lancet 2: 1134, 1977.
100. Gamerre M, Brajon R: Anticoagulants et grossesse. J Gynecol Obstet Biol Reprod (Paris) 6: 829, 1977.
101. Limet R, Grondin CM: Cardiac valve prostheses, anticoagulation, and pregnancy. Ann Thorac Surg 23: 337, 1977.
102. Raivio KO, Ikonen E, Saarikoski S: Fetal risks due to warfarin therapy during pregnancy. Acta Paediatr Scand 66: 735, 1977.
103. Valentine BH, Baker JL: Treatment of recurrent pregnancy hypertension by prophylactic anticoagulation. Br J Obstet Gynecol 84: 309, 1977.
104. Vanlaeys R, Deroubaix P, Deroubaix G, et al.: Les antivitamines K sontelles teratogenes? Nouv Presse Med 6: 756, 1977.
105. Gooch WM, McLendon RE, Parvey LS, et al.: Warfarin embryopathy: longitudinal and postmortem examination. Clin Res 26: 74A, 1978.
106. Pauli RM, Madden J: Warfarin embryopathy. Am J Obstet Gynecol 130: 603, 1978.
107. Robinson MJ, Pash J, Grimwade J, et al.: Fetal warfarin syndrome. Med J Aust 1: 157, 1978.
108. Lutz DJ, Noller KL, Spittell JA, et al.: Pregnancy and its complications following cardiac valve prosthesis. Submitted for publication.
109. Hall JG: Unpublished data.
110. Harrod MJ: Personal communication.
111. Holmes LB: Personal communication.
112. Johnson JF: Personal communication.
113. MacLeod P: Personal communication.
114. Madden J: Personal communication.
115. O'Connor N: Personal communication.
116. Pauli RM: Unpublished data.
117. Pauli RM: Unpublished data.
118. Maeck JVS, Zilliacus H: Heparin in the treatment of toxemia of pregnancy. A preliminary report. Am J Obstet Gynecol 55: 326, 1948.
119. Page EW: Use of heparin in pre-eclampsia. Am J Med 4: 784, 1948.
120. Butler BC, Taylor HC, Graff S: The relationship of disorders of the blood-clotting mechanism to toxemia of pregnancy and the value of heparin in therapy. Am J Obstet Gynecol 60: 564, 1950.
121. DaCunha FAL: Massive haemorrhage following anticoagulant therapy in pregnancy. J Obstet Gynecol Br Emp 59: 521, 1952.
122. Barry GR, Olson MJ: Antepartum thrombophlebitis—a case report. Am J Obstet Gynecol 72: 910, 1956.
123. Ohanesian OD: Antepartum thrombophlebitis. Report of a case. Obstet Gynecol 13: 341, 1959.
124. Mueller MJ, Lebherz TB: Antepartum thrombophlebitis—morbidity with long-term heparin and a proposed regimen of therapy. Obstet Gynecol 34: 874, 1969.
125. Hill WC, Pearson JW: Outpatient intravenous heparin therapy for antepartum iliofemoral thrombophlebitis. Obstet Gynecol 37: 785, 1971.
126. Sher MH: Management of antepartum thrombophlebitis. Am Surg 37: 587, 1971.
127. Whitworth JA, Fairley KF: Heparin in the treatment of preeclamptic toxemia. Perspect Nephrol Hypert 1: 1027, 1973.
128. Shaker K, Amr M, Sliman NA: Uterine contractions due to heparin. Br Med J 4: 408, 1974.
129. Fairley KF, Adey FD, Ross IC, et al.: Heparin treatment in severe preeclampsia and glomerulonephritis in pregnancy. Perspect Nephrol Hyper 5: 103, 1975.
130. Howie PW, Prentice CRM, Forbes CD: Failure of heparin therapy to affect the clinical course of severe pre-eclampsia. Br J Obstet Gynecol 82: 711, 1975.
131. Nilsson IM, Hedner U, Astedt B, et al.: Intravascular coagulation in pregnancy—treatment with heparin. Acta Obstet Gynecol Scand 54: 491, 1975.
132. Saka DM, Marx GF: Management of a parturient with car-

diac valve prosthesis. Anesth Analg (Cleve) 55: 214, 1976.
133. Baskin HF, Murray JM, Harris RE: Low-dose heparin for prevention of thromboembolic disease in pregnancy. Am J Obstet Gynecol 129: 590, 1977.
134. Collins ML, Leal J, Thompson NJ: Tricuspid atresia and pregnancy. Obstet Gynecol 50 (Supp 1): 72s, 1977.
135. (a) Goodman LS, Gilman A, eds: The Pharmacological Basis of Therapeutics, 5th ed, New York, MacMillan Publishing Co. Inc, 1975, p 1354.
(b) McLaurin RL: Parietal cephaloceles. Neurology (Minneap) 14: 764, 1964.
136. Flessa HC, Kapstrom AB, Glueck HI, et al.: Placental transport of heparin. Am J Obstet Gynecol 93: 570, 1965.
137. Bloomfield DK: Fetal deaths and malformations associated with the use of coumarin derivatives in pregnancy. A critical review. Am J Obstet Gynecol 107: 883, 1970.
138. Hirsh J, Cade JF, Gallus AS: Anticoagulants in pregnancy—a review of indications and complications. Am Heart J 83: 301, 1972.
139. Bleyer WA, Hakami N, Shepard TH: The development of hemostasis in the human fetus and newborn infant. J Pediatr 79: 838, 1971.
140. Stenflo J, Suttie JW: Vitamin K—dependent formation of gamma-carboxyglutamic acid. Ann Rev Biochem 46: 157, 1977.
141. Hauschka PV, Lian JB, Gallop PM: Direct identification of the calcium-binding amino acid, gamma-carboxyglutamate, in mineralized tissue. Proc Natl Acad Sci USA 72: 3925, 1975.
142. Hauschka PV, Reid ML, Lian JB, et al.: Probable vitamin K-dependence of gamma-carboxyglutamate formation in bone. Fed Proc 35: 1354, 1976.
143. Hauschka PV, Lian JB, Gallop PM: Vitamin K and mineralization. Trends Biochem Sci 3: 75, 1978.
144. Price PA, Otsuka AS, Poser JW, et al.: Characterization of a gamma-carboxyglutamic acid-containing protein from bone. Proc Natl Acad Sci USA 73: 1447, 1976.
145. Spranger JW, Opitz JM, Bidder U: Heterogeneity of chondrodysplasia punctata. Hum Genet 11: 190, 1971.
146. Curry CJR, Beam CW, Hall BD: Sex-linked inheritance of chondrodysplasia punctata (abstract). Clin Res 26: 193A, 1978.
147. Sheffield LJ, Danks DM, Mayne V, et al.: Chondrodysplasia punctata—23 cases of a mild and relatively common variety. J Pediatr 89: 916, 1976.
148. Hanson JW, Smith DW: The fetal hydantoin syndrome. J Pediatr 87: 285, 1975.
149. Hanson JW, Smith DW: Teratogenicity of anticoagulants. J Pediatr 87: 838, 1975.
150. Roizen NJ: Teratogenicity of anticoagulants. J Pediatr 87: 838, 1975.
151. Pettifor JM, Benson R: Teratogenicity of anticoagulants—reply. J Pediatr 87: 838, 1975.
152. Mountain KR, Hirsh J, Gallus AS: Neonatal coagulation defect due to anticonvulsant drug treatment in pregnancy. Lancet 1: 265, 1970.
153. Bleyer WA, Skinner AL: Fatal neonatal hemorrhage after maternal anticonvulsant therapy. JAMA 235: 626, 1976.
154. Solomon GE, Hilgartner MW, Kutt H: Coagulation defects caused by diphenylhydantoin. Neurology (Minneap) 22: 1165, 1972.
155. Engelberg H: Prolonged anticoagulant therapy with subcutaneously administered concentrated aqueous heparin. Surgery 36: 762, 1954.
156. Denson KWE, Bonnar J: Measurement of heparin in patients receiving subcutaneous heparin therapy. Br J Haematol 30: 139, 1975.
157. Gervin AS: Complications of heparin therapy. Surg Gynecol Obstet 140: 789, 1975.
158. Jick H, Slone D, Borda I, et al.: Efficacy and toxicity of heparin in relation to age and sex. N Engl J Med 279: 284, 1968.
159. Chernoff AI: Anaphylactic reactions following injection of heparin. N Engl J Med 242: 315, 1950.
160. Griffith G, Nichols G, Asher JD, et al.: Heparin osteoporosis. JAMA 193: 91, 1965.
161. Stinchfield FE, Sankaran B, Samilson R: The effect of anticoagulant therapy on bone repair. J Bone Joint Surg (Am) 38A: 270, 1956.
162. Silverstein A: Neurological complications of anticoagulation therapy. Arch Intern Med 139: 127, 1979.
163. Merz WR: Die behandlung der thrombose und lungenembolic mit antikoagulantien. Gynaecologia 130 (Suppl 5): 1,1950.
164. Abbott A, Sibert JR, Weaver JB: Chondrodysplasia punctata and maternal warfarin treatment. Br Med J 1: 1639, 1977.
165. Smith MF, Cameron MD: Warfarin as teratogen. Lancet 1: 727, 1979.
166. Guillot M, Toubas P-L, Meslati J-C, et al.: Embryo-foetopathie coumarinique et maladie des epiphyses ponctuees. Arch Franc Pediat 36: 63, 1979.
167. Stevenson RE, Burton OM, Ferlauto GJ, et al.: Hazards of oral anticoagulants during pregnancy. JAMA (in press).