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Adherence to a guideline for coumarins in pregnancy

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Abstract

Objective: To assess the adherence in daily clinical practice to a guideline for anticoagulation during pregnancy.

Methods: The Dutch anticoagulation clinics developed a pregnancy guideline for anticoagulant therapy in order to avoid foetal exposure to coumarins between the 6th and 9th week of gestation. Anticoagulation was studied in 282 prospectively-registered pregnant women, who were treated by 26 different anticoagulation clinics.

Results: The guideline was adhered to in 93% of treated women. Conforming to the guideline, the majority of patients commenced anticoagulation with heparin in the first trimester ($n = 81$) or started treatment from the second trimester onwards ($n = 168$). At the time of conception, 31 anticoagulated women were on coumarin treatment. In 13 of these patients (42%), coumarins were withdrawn before the 6th gestational week. In two pregnant women coumarin therapy started unintentionally during the first trimester of gestation.

Conclusion: The present study shows that the guideline under study is useful in daily clinical practice. A careful instruction of women of child-bearing age who need medication remains important.

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Introduction

The Thalidomide tragedy dramatically demonstrated the potential risks of medication during pregnancy. Foetal exposure to drugs during critical periods of development can result in structural anomalies, growth restriction, and impaired development of the child. Drug safety during gestation, therefore, remains an important issue.

Anticoagulation during pregnancy must be carefully considered because of disadvantages for both mother and child. Foetal exposure to coumarins from the sixth to the ninth week may cause skeletal abnormalities, the so-called coumarin embryopathy. In addition, *in utero* exposure has been associated with anomalies of the foetal nervous system¹. In contrast to coumarins, heparin does not cross the placenta and is regarded as safe for the foetus. However, heparin treatment has potentially adverse effects for the mother, including osteoporosis after long-term ther-

apy, heparin-induced thrombocytopenia and alopecia². Unfractionated or low-molecular-weight heparin is, nowadays, used for most anticoagulant indications. Its efficacy, however, in pregnant women with prosthetic heart valves is questioned, therefore coumarins are preferred for this indication³.

In the Netherlands, regional anticoagulation clinics monitor oral anticoagulant therapy in out-patients. To improve the safety of anticoagulation during pregnancy, the Federation of Dutch Anticoagulation Clinics developed a 'pregnancy guideline'. These recommendations were published in the journal of the Federation in 1980⁴. Nowadays, this guideline is brought into practice in many European countries for anticoagulation in pregnant women with prosthetic heart valves⁵.

Together with the implementation of the guideline, a prospective registration of anticoagulant therapy during pregnancy was started. On the basis of this registry, we assessed the late effects of coumarins on growth and development⁶. At the same time, we evaluated the adherence to the guideline in daily clinical practice.

Materials and methods

Subjects

Women who were being treated with oral anticoagulants during pregnancy were prospectively registered by the Dutch anticoagulation clinics from 1980 onwards. In addition, we screened the central database facility which automated anticoagulation clinics used for routine care on 'pregnancy'. Included in the study were women treated with oral anticoagulants during pregnancy between January 1982 and December 1990. Eligible women were approached by physicians associated with the anticoagulation clinics, either directly or after consultation with the family's general practitioner. Participants were asked to sign a consent form which included permission to look up medical records from the time of pregnancy and delivery. The study protocol was approved by the Medical Ethics Committee of the University Hospital Groningen.

Pregnancy guideline

The guideline⁴ recommended to avoid the prescription of coumarin derivatives between six and nine weeks of gestation. During the first trimester of pregnancy, anticoagulation with heparin was advised (until about the 14th week).

In women of child-bearing age who need long-term therapy with coumarins, prescription of the short-acting derivative acenocoumarol (Sintrom®) was recommended. These women had to be instructed to present for pregnancy testing as soon as possible, so that coumarins could be replaced by heparin before the sixth gestational week.

During the second and third trimester of pregnancy, coumarin derivatives were regarded as the drugs of

first choice for long-term anticoagulation. To avoid bleeding complications around parturition, the short-acting derivative acenocoumarol was preferred. The guideline recommended to substitute heparin for coumarins from the 36th week onwards.

Methods

Information about anticoagulant therapy during pregnancy was obtained from the pregnancy registration, and was completed with information from anticoagulation clinics and medical records. We looked for data about the indication of anticoagulant therapy, the prescribed coumarin derivative, the date at which treatment with heparin and coumarin derivatives was started and withdrawn, and the date of delivery. The first day of the last menstrual period was used as reference date for duration of pregnancy.

The analysis focussed on anticoagulant treatment during three periods of pregnancy: a) the first trimester, including the time prior to conception; b) the second and third trimester; and c) before expected childbirth. Since pregnancy data do not follow a normal distribution, statistics included the descriptive measures median, range and interquartile range of the gestational weeks at which treatment was started and withdrawn. Duration of treatment was expressed by means and confidence intervals. The analyses were carried out with the help of SPSS⁷.

Results

Subjects

In the period studied, 452 pregnant women were registered by 26 anticoagulation clinics; 314 were enrolled with a registration form and 138 women were registered in the central database facility. Due to incomplete personal data at the time of enrolment, 55 women could not be traced, and in 14 cases the general practitioner discouraged contact with the family because of social circumstances. From the remaining 383 women, 308 gave written informed consent (response rate 80%). The mean age of the participating women was 29 years (range 25 to 33 years). Exact data about anticoagulant therapy during pregnancy could be traced in 282 (92%) of these women. Indications for anticoagulant therapy during pregnancy were treatment ($n = 59$) and prophylaxis ($n = 191$) of thromboembolic events, hereditary thrombophilia ($n = 9$), artificial heart valve ($n = 10$), and a group of incidental causes like antiphospholipid antibody syndrome, trauma, and surgery ($n = 8$); for 6 cases the indication was unknown.

Anticoagulation during the first trimester

During the first 14 weeks of gestation, 114 women (40%) received anticoagulant treatment. Conforming to the recommendation to avoid coumarins in this part of pregnancy, the majority of these women ($n = 81$) received heparin.

However, 33 women were treated with coumarins, 31 of them using coumarin derivatives at the time of conception (Figure 1). Indications comprised long-term anticoagulant prophylaxis because of an artificial heart valve ($n = 10$), hereditary thrombophilia ($n = 3$), history of thromboembolic complications ($n = 3$), systemic lupus erythematosus with throm-

boembolic manifestations ($n = 1$), and femoropopliteal bypass surgery ($n = 1$) (Figure 1, cases 1 to 18). In addition, 13 women conceived while they were on treatment for a deep venous thrombosis ($n = 5$) or pulmonary embolism ($n = 8$) (Figure 1, cases 19 to 31). In accordance with the recommendations, 27 (85%) pregnant mothers received the short-acting coumarin derivative acenocoumarol.

Conforming to the guideline, coumarins were replaced by heparin before the 6th gestational week in 13 of 31 (42%) patients. In 16 women, heparin was introduced in or after the 6th week, whereas in 2 (6%) patients, acenocoumarol was not replaced by heparin at all (Figure 1, cases 17 and 25).

Unfortunately, 2 patients started anticoagulant prophylaxis with acenocoumarol during the first trimester (Figure 1, cases 32 and 33). One of these women was treated after orthopaedic trauma and surgery. In this patient, treatment started in the 8th gestational week and was withdrawn in the 12th week when gestation was recognized.

Indications for anticoagulant therapy in the heparin-treated patients ($n = 81$) were treatment ($n = 11$) or prophylaxis ($n = 70$) of thromboembolic complications.

Anticoagulation during the second and third trimester

Of the 114 women treated with anticoagulants during the first trimester, 3 patients remained on heparin therapy until the end of pregnancy and in 5 women anticoagulation was withdrawn. Throughout the first trimester 3 women continued coumarins; the remaining 103 women resumed or started coumarin therapy between the 11th and the 26th week of pregnancy (median: 16th week; interquartile range 14th to 17th week) (Figure 2). The week at which coumarins were

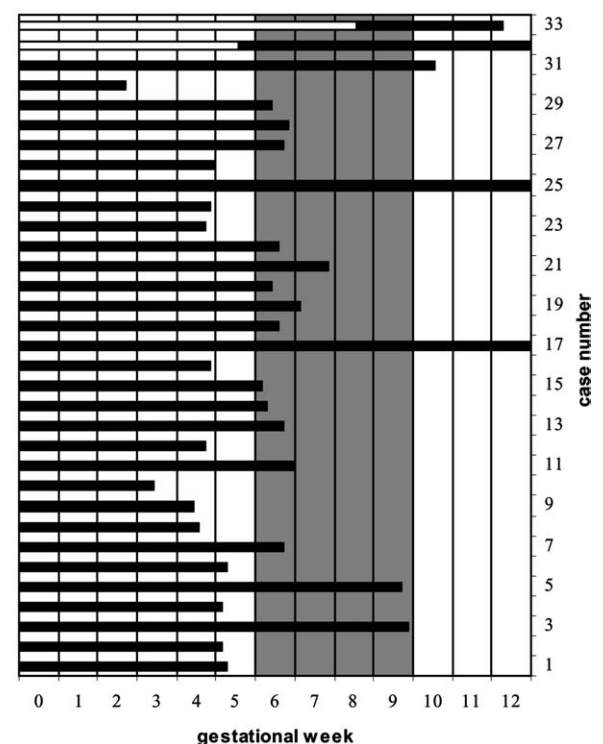


Figure 1 Coumarin use during the first trimester of pregnancy ($n = 33$).

resumed did not differ between the anticoagulation clinics.

In addition, 168 women started anticoagulation with coumarins in the second or third trimester of pregnancy (Figure 2). The gestational age at which coumarin therapy started in these pregnant mothers ranged from 11 to 34 weeks (median: 21 weeks; interquartile range 16 to 26 weeks). Indications included treatment of a thromboembolic event during the current pregnancy ($n = 48$) or prophylaxis of thromboembolic complications in high-risk patients ($n = 116$). In four pregnant women, the indication could not be traced.

Conforming to the recommendation to give preference to the short-acting derivative, 234 (85%) of the 274 women were treated with acenocoumarol during the second and third trimester. Phenprocoumon was prescribed in 32 patients, 17 of which were treated by the same anticoagulation clinic. This clinic prescribed phenprocoumon in 17 of the 47 (36%) women they treated. Six women switched derivative during pregnancy and in two cases the coumarin derivative could not be traced.

The mean duration of coumarin prescription was 18 weeks (CI_{95} : 17 to 19 weeks) for prophylactic and 11 weeks (CI_{95} : 10 to 13 weeks) for therapeutic indications.

Withdrawal of coumarin treatment before parturition

In accordance with the guideline, in 266 (97%) of the 274 women coumarin treatment was discontinued before parturition started. The time at which coumarins were withdrawn ranged from the 28th to the 40th week with a median at the 36th week (Figure 2). We found no differences between the anticoagulation clinics. In 8 (3%) women, parturition started while coumarins were not discontinued yet. In these women, labour started prematurely at a median gestational age of 35.5 weeks (range: 32 to 37 weeks). After vitamin K supplementation, delivery was uncomplicated in all eight women.

Discussion

In our study, the clinical practice of anticoagulation during pregnancy adhered very well to the stated rec-

ommendations. Clearly, an important part of the guideline was to avoid coumarin exposure of the foetus between the sixth and ninth week of gestation. This was adhered to in 93% of the treated women. Of the women who used coumarins at the time of conception, substitution with heparin before the 6th week succeeded in 42% of cases. This underscores the fact that women on treatment with coumarins should be extensively instructed about the foetal risks of coumarin derivatives and need to be encouraged to report a pregnancy as soon as possible.

In a previous paper, we described a large cohort study in which we investigated growth and long-term development of coumarin-exposed children in comparison to non-exposed controls⁶. No major abnormalities were found. For the vast majority of children there was no significant effect on growth and long-term development. However, the risk for a combination of two or more minor abnormalities was higher for the exposed children. In addition to this cohort study, we evaluated the adherence to the used pregnancy guideline. Although the data are historic, we feel they are still instructive since the recommendations of the guideline are used for some well-defined indications during pregnancy. Heparin treatment carries a substantial risk for both valve thrombosis and bleeding complications in pregnant women with artificial heart valves^{3, 8}. In this situation, coumarins are preferred and the studied guideline is applied in many European countries^{5, 9}.

In the period studied, 71 anticoagulation clinics served the Dutch population. The evaluation of adherence to the pregnancy guideline included 26 clinics extended over the country. Although this is a selection of anticoagulation clinics, we feel their policy in clinical practice did not differ from the other clinics. Moreover, they represent more than one third of all anticoagulation clinics in The Netherlands.

In general, there is concern about the impact of guidelines on physician behaviour. Important factors that are known to influence physicians not to adhere to guidelines include lack of familiarity with the guideline and lack of outcome expectancy of the stated recommendations¹⁰. Factors that could have contributed to the high percentage of compliance in this study are the thorough discussion with different medical experts before elaboration and the publication of the guideline in a Dutch journal accessible to the target group of physicians. In addition, the guideline did apply to a specific clinical situation in which physicians are more aware of the potential dangers of therapeutic strategies.

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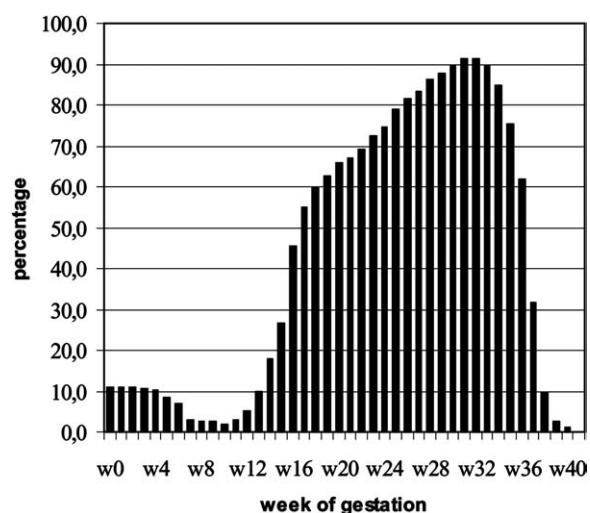


Figure 2 Percentage of pregnancies in which coumarins were prescribed per week of gestation.

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References

- 1 Van Driel D, Wesseling J, Sauer PJJ, Touwen BCL, Van der Veer E, Heymans HSA. Teratogen update: fetal effects after in utero exposure to coumarins. *Teratology* 2002; 66: 127–40.
- 2 Nelson-Piercy C. Hazards of heparin: allergy, heparin-induced thrombocytopenia and osteoporosis. *Baillière Clin Obstet Gynecol* 1997; 11: 489–509.
- 3 Hanania G, Thomas D, Michel PL, Garbarz E, Age C, Millaire A et al. Pregnancy and prosthetic heart valves: a French cooperative retrospective study of 155 cases. *Eur Heart J* 1994; 15: 1651–8.
- 4 Stibbe J, van Dijk-Wierda CA. Antistollingsbehandeling in de zwangerschap. [Anticoagulant therapy in pregnancy.] *Trommbus* 1980; 8: 1–6.
- 5 Gohlke-Barwolf C, Acar J, Oakley C, Butchart E, Burckhart D, Bodnar E et al. Guidelines for prevention of thromboembolic events in valvular heart disease. Study Group of the Working Group on Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 1995; 16: 1320–30.
- 6 Wesseling J, Van Driel D, Heymans HSA, Rosendaal FR, Geven-Boere LM, Smrkovsky M et al. Coumarins during pregnancy: long-term effects on growth and development of school-age children. *Thromb Haemost* 2001; 85: 609–13.
- 7 Statistical Package for the Social Sciences version 7.5 for Windows. Chicago, Illinois: SPSS 1997.
- 8 Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J* 1994; 71: 196–201.
- 9 Robin F, Lecuru F, Desfeux P, Boucay V, Taurelle R. Anticoagulant therapy in pregnancy. *Eur J Obstet Gyn Reprod Biol* 1999; 83: 171–7.
- 10 Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PC et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999; 282: 1458–65.