DOI: 10.1111/tog.12075
The Obstetrician & Gynaecologist
http://onlinetog.org
2014;16:7–11

Review

Retinoids and pregnancy: an update

Hannah Browne MBBS,[a] **Gerald Mason** MBChB FRCOG MD,[b] **Thomas Tang** MD MRCOG[c,*]

[a]Specialist Trainee (Year 2) in Obstetrics and Gynaecology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK
[b]Consultant in Feto-Maternal Medicine, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK
[c]Consultant Gynaecologist, Regional Fertility Centre, Belfast Teaching Hospitals NHS Trust, Belfast, UK
*Correspondence: Thomas Tang. Email: t.m.h.tang@leeds.ac.uk

Accepted on 14 October 2013

Key content
- The use and pharmacokinetics of retinoids.
- The main known teratogenic effects of retinoids are face, skull, cardiovascular, nervous system and thymic abnormalities.
- The pregnancy prevention programme must be adhered to when initiating retinoid treatment.
- Effective contraception should be continued for at least one month after cessation of retinoid treatment.
- Management options of pregnant women with recent retinoid use or exposure in early pregnancy; including involvement of the specialist multidisciplinary team.

Learning objectives
- To understand the risk and in particular teratogenesis associated with exposure to retinoids peri-conception.
- To raise awareness of the pregnancy prevention programme.
- To highlight the management options for women who become pregnant with recent retinoid use or exposure in early pregnancy.

Ethical issues
- Termination of pregnancy with peri-conceptual exposure to retinoids.
- Should isotretinoin be used so widely in the childbearing population when we are aware of its teratogenicity?

Keywords: congenital abnormalities / isotretinoin / pregnancy prevention programme / retinoids / teratogen

Please cite this paper as: Browne H, Mason G, Tang T. Retinoids and pregnancy: an update. *The Obstetrician & Gynaecologist* 2014;16:7–11.

Introduction

Retinoids are widely used to treat acne, and are known to be teratogenic. When prescribed in women of childbearing age, a pregnancy prevention programme is implemented. This aims to prevent pregnancy during treatment and for at least one month following cessation. Despite these measures, pregnancy still occurs and patients often find it difficult to decide whether to continue with their pregnancy or to pursue a termination. This is compounded by a lack of literature advising professionals on how to counsel these women appropriately and approach their subsequent antenatal care. This article aims to update readers on retinoids, their use and teratogenic effects. It outlines the pregnancy prevention programme and current ways to advise and care for women in which this fails.

Retinoids

Retinoids comprise a class of compounds that are related chemically to vitamin A. Isotretinoin, a retinoid (13-*cis*-retinoic acid), was discovered in the 1970s and introduced into clinical use in the early 1980s, as Accutane. It reduces sebum secretion and is therefore used in the systemic treatment of nodulo-cystic and conglobate acne, severe acne, scarring acne which has not responded to an adequate course of systemic antibacterials, or acne which is associated with psychological problems.[1]

Isotretinoin is rapidly absorbed following oral administration, is highly bound to plasma protein and is metabolised to 4-oxo-isotretinoin. The elimination half-life of isotretinoin in plasma is 6–36 hours[2] and up to 50 hours for its longest-lived metabolite.[3] Five elimination half-lives are required to achieve safe levels of the drug and its biotransformation products;[4] it is therefore expected that this would be achieved within 2 weeks of the last dose.[3] However, Nulman et al.[4] conducted a study of 16 young adults (11 women and five men) and found a prolonged elimination half-life in one female patient of 167.4 hours. This would mean that a 35-day period would be required until safe levels were achieved.

The dose of isotretinoin that patients receive is dependent on their weight and severity of the condition. It is usually prescribed as 0.5–1.0 mg/kg/day in one or two divided doses. The total treatment course at a standard dose usually ranges

from 4 to 6 months with a total cumulative dose of 120–150 mg/kg.[1] There is no significant correlation between dose and steady state concentration due to large variability in clearance.[4]

Isotretinoin is extremely successful in its treatment of acne. Layton et al.[5] studied 88 patients and found that 85% had clinical improvement following 4 months of treatment. They were followed up for a mean of 9 years post therapy and 61 patients were virtually still clear of the disease.

Epidemiology

Isotretinoin is widely used owing to its success and, as acne most usually occurs in adolescents, many of the recipients are young females. In 1988 it was estimated that up to 60 000 female patients of childbearing age, per year, in the USA were treated with isotretinoin.[6] Data from an audit at a tertiary centre in Leeds demonstrated that isotretinoin was prescribed to 145 women of childbearing age between May and October 2011. Leeds has an approximate population of 160 438 females of childbearing age (15–44 years). Therefore, in a year it would be expected that approximately 1 in every 500 of the childbearing population will be exposed to isotretinoin.[7]

Among these women, it appears that there is a relatively low pregnancy rate. In 2004, a prospective audit by the British Association of Dermatologists reported 16 pregnancies over a 6-month period; it included results from 75% of UK dermatologists.[8] Additionally, a retrospective Canadian study[9] of 8609 women treated with isotretinoin found that 90 became pregnant (1%).

Teratogenicity

Many adverse effects have been associated with isotretinoin use (Box 1).[8] However, extensive evidence demonstrates that the main concern is its teratogenicity when used systemically in pregnancy.[6] Exposure to a teratogenic drug during the pre-embryonic phase of pregnancy (up to day 17 from conception), results either in survival of an intact embryo or in death. During the embryonic phase (days 18–55), cells differentiate and the major organs are developed. If differentiated cells are damaged by teratogens they are often not replaced, and this may result in permanent malformations. The fetal period, day 56 until birth, allows structures including the cerebral cortex and renal glomeruli to continue development, and as a consequence they remain susceptible to damage during this phase.[10]

It is thought that isotretinoin exerts its teratogenic effect by inducing hypervitaminosis A,[11] as it is a synthetic retinoid or vitamin A derivative. Retinoids are involved in the HOX signalling pathways that are used to pattern the branchial arches (pharyngeal arches) during the fourth week of embryonic development. Consequently, it is the derivatives of the pharyngeal arches that are most affected by isotretinoin exposure during pregnancy.[12] The most frequent malformations are craniofacial, central nervous system, cardiovascular and thymic. The most frequently seen malformations are listed in Box 2.[3,13–15]

Box 1. Adverse effects of isotretinoin

- Mood disturbance
- Dryness of skin and mucous membranes
- Facial erythema, eczema, hair loss, photosensitivity, skin fragility, paronychia and pyogenic granuloma
- Myalgia and arthralgia
- Photophobia, impaired night vision and keratitis
- Nausea, colitis and pancreatitis
- Abnormalities of liver function including hepatitis
- Elevation of triglyceride and cholesterol levels
- Bacterial overgrowth, e.g. *Staphylococcus aureus*
- Cutaneous vasculitis
- Acne flare

Box 2. Malformations associated with isotretinoin use

Craniofacial defects:

- ear defects
- eye defects
- cleft palate
- micrognathia (small jaw)
- depressed nasal bridge
- dysmorphism
- ocular hypertelorism (widely spaced eyes)

Central nervous system defects:

- microencephaly
- facial nerve palsy
- hydrocephalus
- cortical and cerebellar defects

Cardiovascular defects:

- Fallot's tetralogy
- septal defects
- transposition of the great vessels and aortic arch hypoplasia

Thymic abnormalities:

- hypoplasia
- aplasia and ectopia

The ear defects characteristic of isotretinoin syndrome include microtia (small ear), anotia (no ear) and stenosis of the external ear canal.[12] Isotretinoin has also been associated with limb reduction,[16] oculomotor nerve synkinesis[13] and neural tube defects.[10]

Up to 60% of babies born without gross malformations may perform poorly in neuropsychological tests, and may have other problems such as mental retardation (up to 30%),[3] learning disabilities and other behavioural dysfunctions.[17]

The overall risks of fetal malformations in liveborn infants exposed to isotretinoin in utero are estimated to be 20–35%. The incidence of spontaneous miscarriage is thought to be 20–40%.[3] Other studies have reported a lower incidence of spontaneous miscarriage and fetal malformations. Bérard et al.[9] reported an 11% incidence of birth defects and a 3% incidence of spontaneous miscarriage; and Lammer et al.[18] demonstrated that 14% had major malformations at birth.

With regard to topical retinoids, there are isolated case reports that propose a link between typical retinoid embryopathy and topical tretinoin use.[19–21] A prospective cohort study[22] compared the rate of malformations among fetuses exposed and unexposed to tretinoin. The 94 tretinoin-exposed cases and their 133 controls were similar demographically, and pregnancy outcome did not differ between cases and controls. Overall, the use of topical retinoid in pregnancy may pose a small additional teratogenic risk, but more evidence is required. Until further information is available we would suggest that topical retinoids should be avoided in pregnancy.[3]

With regard to lactation, it is advised that systemic retinoids be avoided during breastfeeding; however, the amount of the drug in breast milk after topical application is probably too small to be harmful.[1]

Pregnancy prevention programme[8,23]

Isotretinoin was authorised in the USA in 1982 and in the EU in 1983. Initial reports of isotretinoin teratogenicity emerged soon after its release and led to the marketing authorisation holder implementing the first pregnancy prevention programme in 1988.[24] The programme provided educational materials for physicians and patients and funded contraceptive counselling. However, concerns continued and led to Roche, the manufacturer of Accutane, developing a second pregnancy prevention programme in 2002: The System to Manage Accutane Related Teratogenicity (SMART).[24]

These were both voluntary programmes and compliance was poor. Subsequently in 2005 the US Food and Drug Administration launched the mandatory iPLEDGE programme, in which only registered prescribers enrolled in the programme could prescribe isotretinoin to patients who qualified and who had been registered.[25]

The Medicines and Healthcare Products Regulatory Agency introduced a similar programme in the UK in the same year, following the recommendations of the European Medicines Control Agency.[8] This consists of three parts; an educational programme, therapy management and distribution control.

Educational programme

Before prescribing isotretinoin, dermatologists should counsel the patient regarding its teratogenic effects and provide an information leaflet relevant to the brand of drug being prescribed.

Therapy management

Educational material should be provided to the patient and medically supervised pregnancy tests should be undertaken. These should be performed at the time of prescription or in the 3 days preceding, monthly during treatment, and 5 weeks following the end of treatment. Patients should ideally use a hormonal contraceptive as their main form of contraception, e.g. combined oral contraceptive pill, progesterone injection, or implantable devices. This should be combined with a barrier contraceptive and initiated one month prior to the start of treatment and for one month following cessation.

Distribution control

Each prescription is for 30 days of treatment and valid for 7 days.

Management of women who become pregnant

There is a lack of robust evidence regarding management of women who become pregnant following exposure to retinoids. This is likely due to a relatively low incidence of conception, owing to implementation of pregnancy prevention programmes. As a result of limited evidence, there are no guidelines or reliable management pathways for pregnant women. Subsequently, the care of these women is often disjointed, variable and involving different specialties.

Termination of pregnancy is often regarded as the safest option due to the known potent teratogenicity of retinoids. Bérard et al.[9] found that 84% of women who fell pregnant on isotretinoin terminated the pregnancy. Additionally, of the 16 pregnancies reported to the British Association of Dermatologists in 2004, seven resulted in terminations (44%).[8]

Management of women who conceive following recent retinoid use, as opposed to those who become pregnant on isotretinoin, is rather more difficult. Current advice is to allow at least one month following cessation of retinoids before attempting conception. However, studies have shown that isotretinoin and its metabolites can be cleared more quickly than this.

A manufacturer published a report on the outcome of 101 pregnancies in women who discontinued isotretinoin prior to conception. The exact length of time from discontinuation of the drug to conception is not known; however, from 88 prospective cases, 9.1% had spontaneous miscarriages and 5% suffered from congenital abnormalities. This is similar to the incidence of spontaneous miscarriage and major congenital abnormalities in the general population, which is estimated to be 10–20% and 2–3% respectively.[3] In addition, the malformations in the aforementioned

study were not characteristic of retinoid-induced congenital abnormalities.

It has been suggested that safe levels of isotretinoin are achieved within 2 weeks of the last dose.[4] However, more evidence is needed before safely advising women who conceive less than one month post cessation of treatment that their teratogenic effect may be less than those who become pregnant while on treatment.

Termination of pregnancy, although the preferred option, may not be suitable for all women; therefore, counselling should be individualised. Development of a specialised pathway may be appropriate, whereby women are referred to an appropriate caregiver, such as a feto-maternal medicine consultant. Subsequent care will begin with initial counselling as to their individual risk of teratogenicity and a discussion of the available options. Women may decide to pursue a termination of pregnancy immediately; however, others may wish to continue with their pregnancy. Approaches to their subsequent antenatal care could be to identify developing malformations, which may lead to late termination of pregnancy; but primarily to offer support. It must be emphasised, however, that unfortunately not all affected fetuses have significant detects that can be identified on ultrasound. Moreover, long-term developmental problems cannot be predicted.

Whereas there is limited guidance as to definitive antenatal management, additional interventions, investigations and surveillance may supplement routine antenatal care. It has been suggested that high-dose folic acid may reduce the incidence of neural tube defects.[3] However, the extent of its benefit may be limited by the fact that the neural tube closes at day 30 of development (day 44 from last menstrual period)[26] and women often present later than this. Alpha-fetoprotein level at 16–19 weeks may offer an extra indication as to the presence of neural tube defects,[3] although ultrasound imaging at this stage would likely be better for this purpose.

Targeted ultrasound should provide the mainstay of antenatal care. This could include an ultrasound scan at 12 weeks to provide an initial check on anatomy, date the pregnancy and contribute to combined first trimester Down syndrome screening. A 16-week ultrasound scan may again examine the anatomy and provide an initial check of the spine. Further ultrasound scans may be at the 20-week anatomy scan, followed with an echo at 22 weeks. Ultrasound scans following this would likely only serve the purpose of reassurance; however, women need to be aware that the absence of abnormalities on ultrasound scan does not guarantee normality.

Three-dimensional scanning may also be of benefit in cases of isotretinoin teratogenicity as there is a known correlation between exposure and development of craniofacial abnormalities, particularly ear defects.

Ethical issues[27,28]

The ethical issues raised by this article are primarily those surrounding termination of pregnancy. Termination of pregnancy is often a contentious issue, but in the case of potential fetal abnormalities it is justifiable. This is highlighted legally by the UK's 1967 Abortion Act, which allows termination of pregnancy if there is a substantial risk that, if the child were born, it would suffer from such physical or mental abnormalities as to be 'seriously handicapped'.[29]

Isotretinoin's potent teratogenic effects are well described, and, in the absence of structural malformations, the presence of later neurodevelopmental delay cannot be predicted.

Studies have shown that isotretinoin and its metabolites can be cleared relatively quickly and that not all babies are affected. However, realistically where there is such a clear risk, a termination of pregnancy has to be offered after appropriate counselling.

Termination of pregnancy may not be the preferred option for many women due to religious or personal beliefs. In these situations our role as clinicians is to provide appropriate advice, counselling and support through a very difficult time.

Another point to consider is whether isotretinoin should be used so widely in the childbearing population when we are aware of its potent teratogenicity?

The success of isotretinoin as a treatment of acne is well documented, and when the pregnancy prevention programme is adhered to successfully it can be used safely in women of childbearing age.

Informed consent is vital in the prescription process, and women should be educated as to the teratogenicity of retinoids and contraceptive options.

Conclusion

Isotretinoin is an effective treatment for what may be a very distressing condition; however, it is extremely teratogenic. The effect on the fetus results mainly in craniofacial, central nervous system, cardiovascular and thymic abnormalities. To avoid these teratogenic effects, a pregnancy prevention programme should be strictly adhered to in women of childbearing age. However, if pregnancy occurs, appropriate counselling should be provided. This would involve education regarding isotretinoin's teratogenic effects, including an increased risk of spontaneous miscarriage, fetal malformations and developmental delay. Tailored antenatal care within an appropriate setting such as a feto-maternal medicine department will aid families' decision-making and will provide support throughout an extremely difficult time.

Disclosure of interests

None declared.

References

1 British Medical Association and Royal Pharmaceutical Society. *British National Formulary*. London: BMA/RPS; September 2010. p. 716.
2 Hardman JG, Limbird LE. *Goodman and Gilman's Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill; 2001. Vol. **48**, p. 1781–2.
3 National Teratology Information Service. *Use of Isotretinoin in Pregnancy*. 2008 [www.toxbase.org].
4 Nulman I, Berkovitch M, Klein J, Pastuszak A, Lester RS, Shear N, Koren G. Steady state pharmacokinetics of isotretinoin and its 4-oxo metabolite: implications for fetal safety. *J Clin Pharmacol* 1998;**38**:926–30.
5 Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later; a safe and successful treatment. *Br J Dermatol* 1993;**129**:292–6.
6 Strauss JS, Cunningham WJ, Leyden JJ, Pochi PE, Shalita AR. Isotretinoin and teratogenicity. *J Am Acad Dermatol* 1988;**19**:353–4.
7 [www.leeds.gov.uk/Council_and_democracy/Statistics_and_census_information/Census_of_Leeds_2001.aspx]
8 Goodfield MJD, Cox NH, Bowser A, McMillan JC, Millard LG, Simpson NB, Ormerod AD. Advice on the safe introduction and continued use of isotretinoin in acne in the UK 2010. *Br J Dermatol* 2010;**162**:1172–9.
9 Bérard A, Azoulay L, Koren G, Blais L, Perreault S, Oraichi D. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. *Br J Clin Pharmacol* 2007;**63**:196–205.
10 Emerson A. *What should you think about when prescribing to pregnant women? UKMi Medicines Q+A 34.3* [http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Medicines%20Q%20&%20A/QA34_5_PregnancyPrescribing.doc].
11 Geelen JAG, Hypervitaminosis A. induced teratogenesis. *CRC Crit Rev Toxicol* 1979;**6**:351–75.
12 Dolan SM. Isotretinoin and pregnancy—a continuing risk for birth defects. *Medscape Ob/Gyn* 2004;**9**(2).
13 Morrison DG, Elsas FJ, Descartes M. Congenital oculomotor nerve synkinesis associated with fetal retinoid syndrome. *J APPOS* 2005;**9**:166–8.
14 Braun JT, Franciosi RA, Mastri AR, Drake RM, O'Neil BL. Isotretinoin dysmorphic syndrome. *Lancet* 1984;**1**:506–7.
15 Hill RM. Isotretinoin teratogenicity. *Lancet* 1984;**1**(8392):1465.
16 McBride WG. Limb reduction deformities in child exposed to isotretinoin in utero on gestation days 26–40 only. *Lancet* 1985;**325**:1276.
17 Rosa FW. Retinoic acid embryopathy. *N Engl J Med* 1986;**315**:262.
18 Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, et al. Retinoic acid embryopathy. *N Engl J Med* 1985;**313**:837–41.
19 Lipson AH, Collins F, Webster WS. Multiple congenital defects associated with maternal use of topical tretinoin. *Lancet* 1993;**341**(8856):1352–3.
20 Camera G, Pregliasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet* 1992;**339**:687.
21 Navarre-Belhassen C, Blanchet P, Hillaire-Buys D. Multiple congenital malformations associated with topical tretinoin. *Ann Pharmacother* 1998;**32**:505.
22 Shapiro L, Pastuszak A, Curto G, Coren G. Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet* 1997;**350**:1143.
23 Medicines and Healthcare Products Regulatory Agency Approved Text. Brand name (isotretinoin) Pregnancy Prevention Programme Pharmacist's guide to dispensing isotretinoin[www.mhra.gov.uk].
24 Crijns HJMJ, Straus SM. Gispen-de Wied C, de Jong-van den Berg LT. Compliance with pregnancy prevention programmes of isotretinoin in Europe: a systematic review. *Br J Dermatol* 2011;**164**:238–44.
25 US Food and Drug Administration. iPLEDGE programme[www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformation forPatientsandProviders/ucm094307.htm].
26 Jones KL. *Smith's Recognisable Patterns of Human Malformations*. 4th edn. Toronto: Saunders; 1988. p. 1.
27 BBC Ethics Guide. When is the foetus 'alive'? [www.bbc.co.uk/ethics/abortion/child/alive_1.shtml].
28 Dickinson D. *Ethical Issues in Maternal–Fetal Medicine*. Cambridge: Cambridge University Press; 2002.
29 Abortion Act 1967. *Chapter 87*. London: The Stationery Office; 1967 [www.legislation.gov.uk].

