Contraception for individuals with sickle cell disease: a systematic review of the literature

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CRD summary
This review assessed the safety of hormonal and intrauterine contraceptive use in women with sickle cell disease and concluded that despite limited data there was no evidence to suggest an increased risk of clinical complications. Limitations in the review methods and evidence presented suggest that the authors’ conclusions should be interpreted with some caution as they may not be reliable.

Authors' objectives
To examine the risk of adverse outcomes from hormonal and intrauterine contraceptive use in women with sickle cell disease.

Searching
PubMed was searched for relevant studies. The search was restricted to studies published in peer-reviewed journals between 1966 and March 2011. No language restrictions were applied. Search terms were provided. Reference lists of relevant articles were examined for further studies.

Study selection
Studies that examined health outcomes among women with sickle cell disease who were using hormonal contraceptives or intrauterine contraceptive devices were included. Any study designs except for case series and case reports were included. Studies of women with sickle cell trait and studies of women who used exogenous hormones for purposes other than contraception were excluded. Clinical outcomes assessed included venous thromboembolism and number, frequency and severity of sickle crises. Potential surrogate markers for the risk of sickle cell crises were included, such as haemoglobin F, reticulocyte count, red blood cell (erythrocyte) deformability and mean clogging rate. Studies that included only biochemical markers not clearly related to venous thromboembolism risk or risk of sickle crises were excluded.

Included studies were published between 1982 and 2011 and were undertaken in Jamaica, UK, Nigeria, Panama, USA and Brazil. Studies included women aged 13 to 41 or described as being of reproductive age with homozygous sickle cell disease (haemoglobin SS), haemoglobin SC, haemoglobin S beta thalassaemia (thalassaemia with one copy of the gene for sickle cell disease and one for beta thalassaemia) or sickle cell haemoglobinopathies (including sickle cell thalassaemia). Contraceptives used included progestin-only contraceptives (Depo-Provera, progestin-only implants and progestin-only pill), combined oral contraceptives and intrauterine devices. The controlled trials compared more than one type of contraception and/or contraception users to non-users.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Study quality was not formally assessed but studies were graded according to the United States Preventive Services Task Force grading system and an overall summary of internal validity was given.

Data extraction
Data were extracted using a standard abstraction form.

The authors did not state how many reviewers extracted data.

Methods of synthesis
A narrative review was undertaken due to variation in outcomes reported. Results were summarised according to contraceptive method (progestin-only methods, combined hormonal methods and intrauterine contraceptive devices) and with clinical outcomes and haematologic or biochemical parameters assessed separately.

Results of the review
Nine studies (one randomised crossover trial, two non-randomised controlled trials, two prospective descriptive studies and four cross-sectional studies) were included with 391 participants (one study included 250 women with sickle cell disease, including 20 who were using contraception). Sample sizes ranged from 10 to 164. Methodological quality was judged as fair to poor.

Progestin-only contraception (evaluated in nine studies) had no effect on frequency of sickle crises or other adverse events and showed significant improvements in haematologic parameters in two out of seven studies. The randomised trial (25 participants) found fewer episodes of bone pain and fewer patients with bone pain using Depo-Provera compared to saline injections (p=0.05).

Four studies evaluated combined hormonal contraception. One non-randomised controlled trial suggested an improvement in clinical outcomes that was not supported by the results of a cross-sectional study. The two remaining cross-sectional studies found no significant effects on haematologic parameters.

Use of intrauterine contraceptive devices was assessed in one cross-sectional study that reported no serious adverse events and no intrauterine contraceptive device users who discontinued use due to side effects.

**Authors’ conclusions**
The authors’ concluded that data were limited but there was no evidence to suggest that hormonal contraceptive use among women with sickle cell disease was associated with an increased risk of clinical complications.

**CRD commentary**
The aim and inclusion criteria for this review were clearly specified. The search was limited to one electronic database, was restricted to peer-reviewed literature and made no attempt was made to identify grey literature so there was a risk of publication bias. No language restrictions were imposed. Some study details were provided in table format. Results per group and p-values for differences between groups were not given for the controlled studies. No formal validity assessment was reported. Some comments related to validity and an overall summary of quality was given, which suggested that quality was somewhat limited.

Limited information was given on the review methods which left potential for reviewer bias. The narrative approach to study synthesis was appropriate given the differences between studies. Limitations in the review methods and limitations in the evidence (such as small sample sizes and lack of comparison groups and significance values to enable confirmation of the findings) suggest that the authors’ conclusions should be interpreted with some caution as they may not be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that their results supported 2010 guidance from the United States Medical Eligibility Criteria for Contraceptive Use which stated that the benefits of using the combined contraceptive or intrauterine devices usually outweighed the risks for women with sickle cell disease; no restrictions were placed on the use of progestin-only contraceptives in these women.

**Research:** The authors stated that further research was needed to determine whether combined hormonal contraceptive use increased the risk of venous thromboembolism in women with sickle cell disease relative to women without sickle cell disease.

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