# Prenatal Prevention for Severe Thalassemia Disease at Srinagarind Hospital

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***Objective:*** *To evaluate the results and cost-effectiveness of prenatal prevention measurement in severe thalassemia diseases at Srinagarind Hospital.*
***Study design:*** *Descriptive study.*
***Setting****: Antenatal care (ANC) Clinic, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University.*
***Subjects****: 1,498 thalassemic screened pregnant women first presenting at ANC Clinic at gestational age less than 17 weeks.*
***Material and Method:*** *Medical records of thalassemic screened pregnant women between February 2002 and February 2005 were analyzed. Those with a value of mean corpuscular volume (MCV) less than 80 fl, or positive dichlorophenol indophenol precipitation test (KKU-DCIP Clear Reagent Kit) underwent hemoglobin (Hb) typing by high performance liquid chromatography (HPLC) together with thalassemia investigation (complete blood count, MCV and Hb typing) of their husbands and to identify couples at risk of 3 severe thalassemia diseases; Hb Bart's hydrops fetalis, homozygous ,-thalassemia and ,-thalassemia/ Hb E disease. Then they were advised to undergo DNA analysis and, if they had fetal risk, appropriate prenatal diagnosis was offered*
***Main outcome measure:*** *Number of affected fetuses detected by prenatal diagnosis.*
***Results:*** *Nine hundred and ninety six pregnant women (66.49%) were positive on screening. Of these, 642 (64.46%) had thalassemia investigation done with their spouses. There were 19 couples at risk (1.27%of total screened pregnant women) for having fetal severe thalassemia disease from initial laboratory results. Most of them were ,-thalassemia/ Hb E diseases. We found only 10 pregnant women (52.63%) that had undergone prenatal diagnosis. The consequent results were two affected fetuses (20%), one was Hb Bart's hydrops fetalis, and the other was ,$^{o}$-thalassemia/ Hb E disease. In these cases, their parents decided to discontinue the pregnancy. Our prevention program could save 1.14 million bahts for the cost of treatment in two prevented severe thalassemia cases.*
***Conclusion:*** *The prenatal prevention program of severe thalassemia disease at Srinagarind Hospital can effectively detect affected fetuses and reduce severe thalassemia disease, which is a major health problem in Thailand.*

***Keywords:*** *Prenatal screening, Prenatal diagnosis, Thalassemia*

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Thalassemia is the most common hematological genetic disease in Thailand. Approximately 30-40% of the populations are carriers of thalassemia and have abnormal hemoglobin[1]. It is estimated that 20-40% of the population are α-thalassemia carriers and 3 to 9% are carriers of ,-thalassemia[2]. Hb E ranges from 8 to 60%, but in the northeast of Thailand, the prevalence of Hb E ranges from 20-40%[3]. The high prevalence of carriers leads to many births of newborns and children with severe thalassemia diseases, i.e. Hb Bart's hydrops fetalis, homozygous ,-thalassemia, and ,-thalassemia/ Hb E disease. Direct cost for the management of one major thalassemia patient who lives until 10-30 years old is about 1.2-6 million Bahts[4]. In case of Hb Bart's hydrops fetalis, their mother often suffer from obstetric complications such as preeclampsia, dystocia, postpartum hemorrhage due to a large placenta, retained placenta, and the psychological burden of carrying a non-viable fetus[1,5]. Therefore, these three severe thalassemia diseases need to be prevented, especially by a prenatal approach[1].

The program for prenatal prevention of severe thalassemia diseases has been implemented at Srinagarind Hospital since February 2002. There is still no evaluation of the results and cost-effectiveness of this program.

**Material and Method**

This study was approved by The Khon Kaen University Ethics Committee for Human Research. For this retrospective study, we included 1,498 thalassemic screened pregnant women whose gestational age (GA) of less than 17 weeks first presenting at Antenatal care Clinic, Department of Obstetrics and Gynecology, Srinagarind Hospital, Khon Kaen University, between February 2002 and February 2005. The medical records of pregnant women were reviewed and selected for the study. Pregnant women who had mean corpuscular volume (MCV) of less than 80 fl or positive dichlorophenol indophenol precipitation test (KKU-DCIP Clear Reagent Kit)[6] were given genetic counseling about thalassemia and had hemoglobin (Hb) typing by using the automated high performance liquid chromatography (HPLC). The positive screened pregnant women were requested to bring their husbands for thalassemia investigation (complete blood count, MCV and Hb typing) and had follow-up at the Genetic counseling Clinic. If couples were identified as having risk for one of the three severe thalassemia diseases, they would be counseled for DNA analysis before the prenatal diagnosis (PND) was performed. Identification of $\alpha^{o}$-thalassemia, β-thalassemia, and Hb E gene were performed using PCR and related techniques described elsewhere[7-9] Those at true risk for having fetal severe thalassemia disease, PND such as chorionic villus sampling, amniocentesis, fetal blood sampling or serial ultrasonography for early detection of fetal hydrops[10], was offered. If they indeed had an affected fetus, they would receive further counseling with respect for termination of pregnancy. The protocol of prenatal prevention program is shown in Fig. 1.

The main outcome measurement was the rates of positive screened pregnant women, husband thalassemia investigation, high risk couples, acceptance of PND, affected fetuses and termination of pregnancy. In this report, we presented our main outcome results as percentage. We also calculated all payments used in this program and analyzed the cost-effectiveness.

**Results**

The average gestational age at first ANC visit was 9.73 $\pm$ 2.08 weeks. There were 996 positive tests (66.49%) from the 1,498 screened pregnant women. Four hundred and eighty one cases of thalasemia carriers were heterozygous Hb E (32.11%). Ninety-four cases (6.28%) were suspected of α-thalassemia 1 trait. Eighteen cases (1.2%) were β-thalassemia trait. Six hundred and forty two husbands (64.46%) had thalassemia investigation. We found 19 couples at risk (1.27% of total screened pregnant women) for having fetal severe thalassemia diseases from initial laboratory results. Thirteen of 19 couples had fetal risk of β-thalassemia/ Hb E diseases (68%) and six couples had risk of Hb Bart's hydrops fetalis (32%). Six couples (31.58%) at risk of β-thalassemia/Hb E diseases refused DNA analysis and PND. The reasons were that three couples were maternal $\beta^{+}$-thalassemia/Hb E disease, which is not a severe form, two couples accepted having affected children, and one couple was lost follow up and came back to ANC at advanced gestational age. Among 13 couples who performed DNA analysis before PND, we could identify 10 couples (52.63% of 19 couples at risk from initial laboratory results) of true fetal risks. Five cases (50%) underwent cordocentesis, four cases (40%) had chorionic villus sampling, and one case (10%) had amniocentesis.The results of PND showed that there were four cases of normal fetuses, three cases of $\beta^{\circ}$-thalassemia trait, one case of α-thalassemia 1 trait $\beta^{\circ}$-thalassemia/Hb E disease, and Hb Bart's hydrops fetalis. All affected fetuses (100%) were terminated after proper counseling. The results of this study are shown in Fig. 2. As for the cost of prevention, we found that it

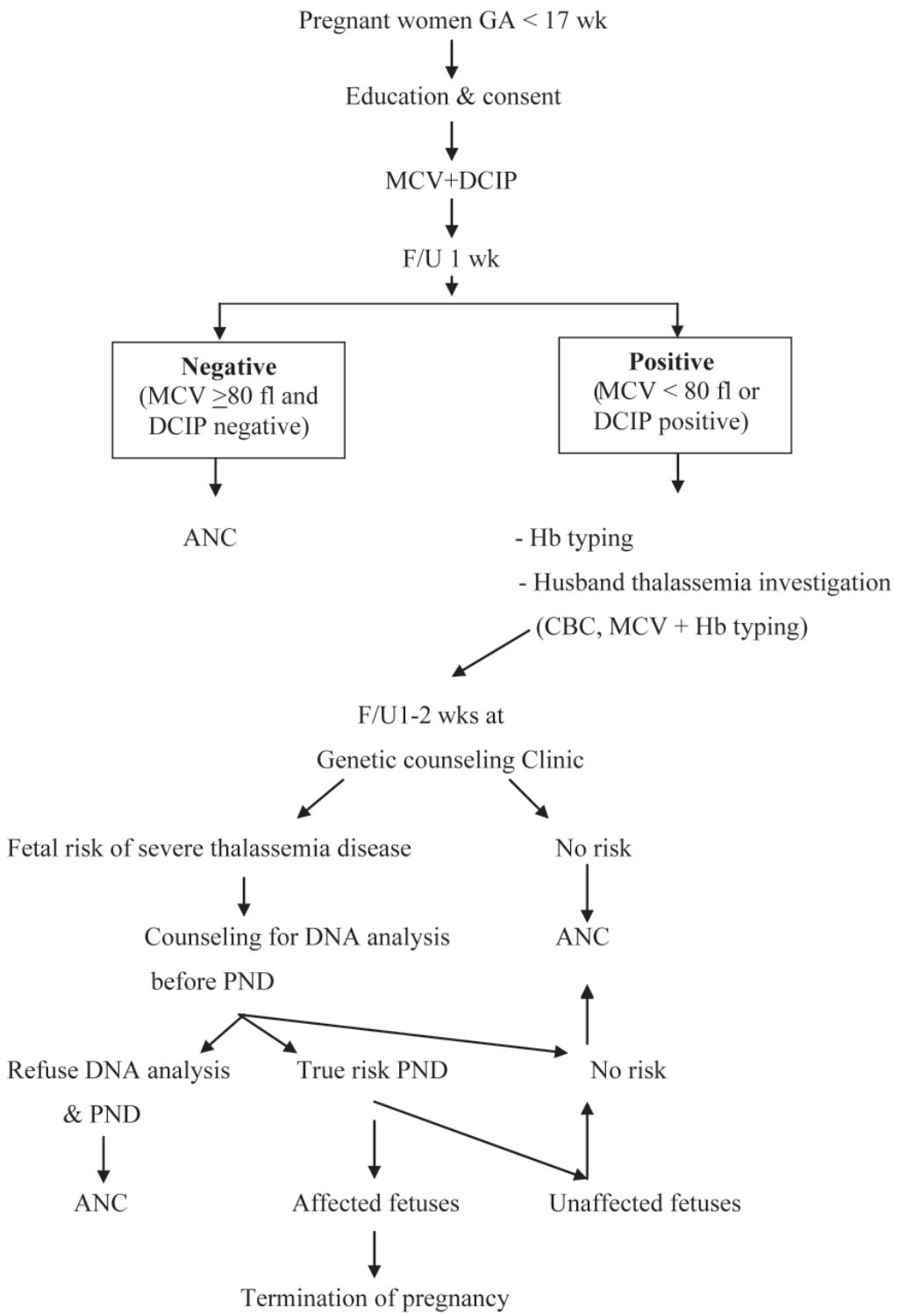


**Fig. 1** The protocol of prenatal prevention program for severe thalassemia disease at Srinagarind Hospital
NB: GA = gestational age, MCV = mean corpuscular volume, DCIP = dichlorophenol indophenol precipitation, F/U = follow up, CBC = complete blood count, Hb = hemoglobin, ANC = antenatal care clinic, PND = prenatal diagnosis

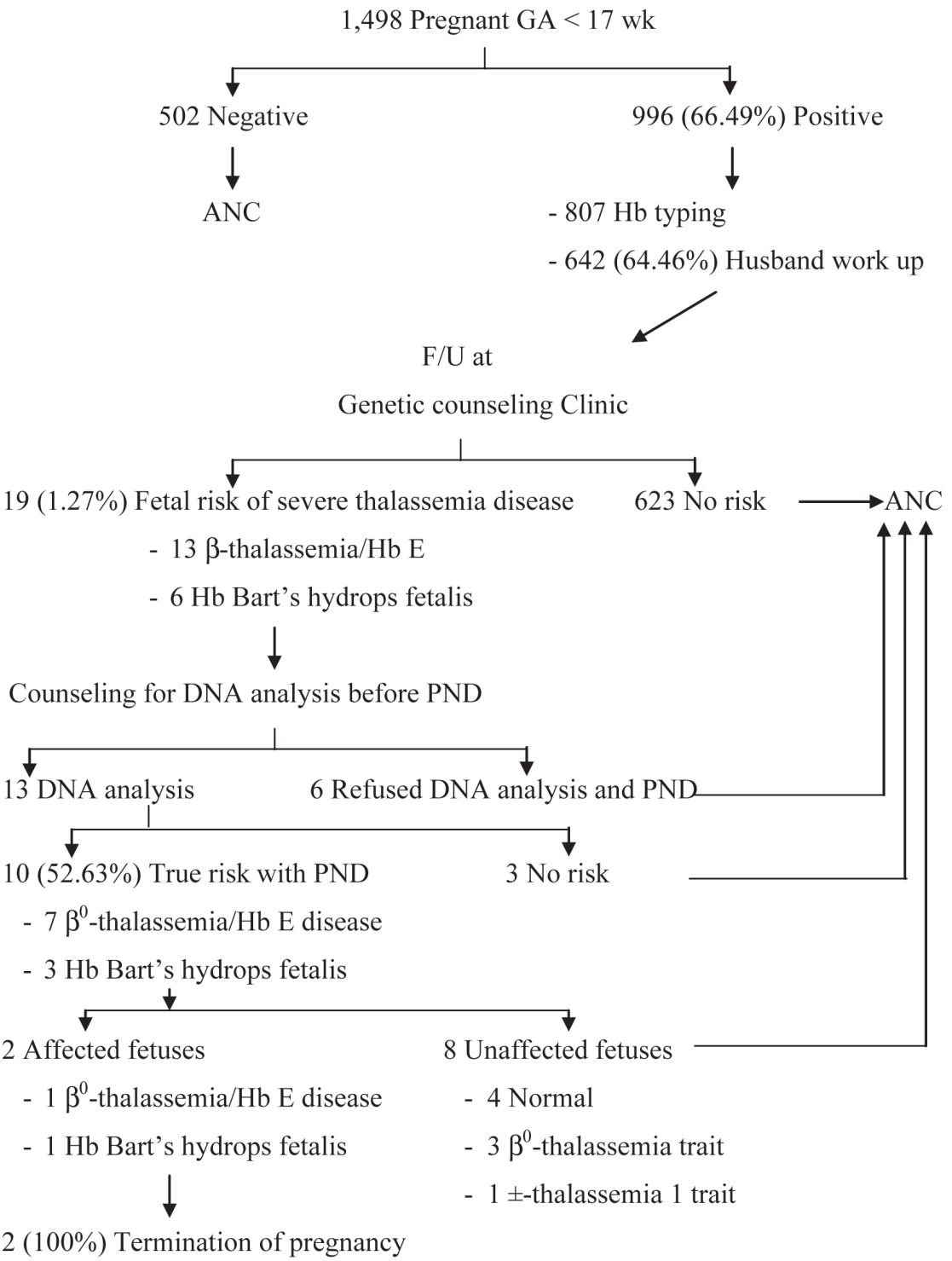


**Fig. 2** Results of the prenatal prevention program of severe thalassemia disease at Srinagarind Hospital
NB: GA = gestational age, F/U = follow up, PND = prenatal diagnosis
CBC = complete blood count, Hb = hemoglobin, ANC = antenatal care clinic

cost 679,400 Bahts (laboratory cost = 663,100 Bahts, PND cost = 13,300 Baths, and termination of pregnancy = 3,000 Bahts) for this program to prevent two cases of severe thalassemia diseases. There was one with Hb Bart's hydrops fetalis and the other with β°-thalassemia/Hb E disease. If we had no prevention program, it would have cost 1,822,000 Bahts for the treatment of these two cases. Therefore, we have saved 1,142,600 Bahts.

## Discussion

In our study, we included pregnant women whose GA was less than 17 weeks because there was enough time for further investigation if there was a positive screening test. This took an additional 8 weeks until termination of pregnancy was held at GA 24 weeks. There are many tests used for thalassemia screening and there are different tests used in different places, but at Srinagarind Hospital, we used MCV and DCIP because we have an automatic electronic blood cell counter, which can automatically calculate both CBC and MCV at the same time[11]. Furthermore, the sensitivity and specificity of this combination tests were 100% and 76.2%[12]. Our study found 996 cases (66.49%) of positive screening test. This was higher prevalence when compared to Tongsong T, et al (28.7%)[1]. This may be because in the northeast of Thailand has higher prevalence of heterozygous Hb. In our study, 481 cases (32.11%) were Hb E trait. 121 cases (25.16%) of this had normal MCV, compared with a study of Sukpanichnant S, et al[13] that was 30.4%. Therefore, it was essential to perform DCIP test in detection of Hb E and unstable Hb eventhough MCV is normal[14,15].

There were 19 couples (1.27% of total screened pregnant women) at risk from initial laboratory results in our study, which was similar to 0.86% of Jaovisidha A, et al[16] but different from the higher rate of 2.8% of Kor-anantakul, et al[17] and 2.23% of Tongsong T, et al[1].

Our institute has a facility for DNA analysis that can confirm diagnosis of couples at risk before prenatal diagnosis is performed. In this study, we could eliminate three cases of patients for unnecessary PND. Thus, DNA analysis is a very useful method in our program. In our study, chorionic villus sampling was performed in four cases (40%), which was different from study of Tongsong T, et al[1] where cordocentesis was performed in all cases. We could do chorionic villus sampling in this study because we have DNA analysis for fetal tissue. Diagnosis and diagnostic test was performed in husbands leading to detection of couple at risk in early pregnancy.

This program could prenatally prevent two cases of severe thalassemia, one case of Hb Bart's hydrops fetalis and the other of β°-thalassemia/Hb E disease. We found that we could save the cost of treatment in these two cases, which were 1,142,600 Bahts (total cost of treatment was 1,822,000 Bahts compared to the total cost of prevention in our program at 679,400 Bahts)[18,19]. Similarly, Wanapirak C could detect 80 cases of fetal severe thalassemia diseases and save nearly 220,000,000 Bahts from the prevention program[15].

Our study collected retrospective data. One of the limitations in this type of study was incomplete data records such as husband investigation rate that appeared to be lower in this study than in other studies. In our study, we reported prevalence of suspected α-thalassemia 1 trait that was probably higher than the true prevalence because we did not confirm every case by DNA analysis.

We concluded that two cases of severe thalassemia diseases were prevented. When costs as opposed to charges are considered and the cost of long-term care for severe thalassemia cases is taken into account, prenatal prevention program is likely to be associated with a significant cost saving for the health care system.

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## การป้องกันโรคธาลัสซีเมียชนิดรุนแรงก่อนคลอดที่โรงพยาบาลศรีนครินทร์

**ถวัลย์วงค์ รัตนสิริ, จุฑารัตน์ เจริญทอง, รัตนา คำวิลัยศักดิ์, ยศสมบัติ จังตระกูล, สุพรรณ ฟู่เจริญ, จำรัส วงค์คำ, พิไลวรรณ กลีบแก้ว, กนก สีจร**

***วัตถุประสงค์:*** *เพื่อศึกษาผลและประสิทธิผล-ต้นทุนในการป้องกันโรคธาลัสซีเมียชนิดรุนแรงก่อนคลอดที่โรงพยาบาลศรีนครินทร์*

***วิธีการศึกษา:*** *การศึกษาเชิงพรรณนา*

***สถานที่ทำการศึกษา:*** *คลินิกฝากครรภ์ โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น*

***วัสดุและวิธีการ:*** *สตรีตั้งครรภ์อายุครรภ์น้อยกว่า 17 สัปดาห์ที่มาฝากครรภ์ครั้งแรกและได้รับการตรวจกรองก่อนคลอดโรคธาลัสซีเมียจำนวน 1,498 คน ได้วิเคราะห์เวชระเบียนของสตรีตั้งครรภ์ที่ได้รับการตรวจกรองก่อนคลอดโรคธาลัสซีเมียระหว่างเดือนกุมภาพันธ์ พ.ศ. 2545 ถึงเดือนกุมภาพันธ์ พ.ศ. 2548 สตรีตั้งครรภ์ที่มีค่าเฉลี่ยปริมาตรเม็ดเลือดแดง (mean corpuscular volume: MCV) ต่ำกว่า 80 เฟมโตลิตร หรือผลตรวจ dichlorophenol indophenol precipitation test (KKU-DCIP Clear Reagent Kit) ให้ผลบวก จะได้รับการตรวจยืนยันหาชนิดของฮีโมโกลบิน (hemoglobin typing) ด้วยวิธี high performance liquid chromatography (HPLC) ร่วมกับตรวจ complete blood count ค่าเฉลี่ยปริมาตรเม็ดเลือดแดงและชนิดของฮีโมโกลบินของสามี เพื่อหาคู่เสี่ยงต่อโรคธาลัสซีเมียชนิดรุนแรง 3 โรค คือ Hb Bart's hydrops fetalis, homozygous $\beta$-thalassemia และ $\beta$-thalassemia/ Hb E disease คู่เสี่ยงจะได้รับ การตรวจวิเคราะห์ ดี เอ็น เอ (DNA analysis) และถ้าพบว่าทารกในครรภ์เสี่ยงต่อโรคธาลัสเมียชนิดรุนแรงดังกล่าวจริง ก็จะได้รับคำปรึกษาเพื่อตรวจวินิจฉัยก่อนคลอดต่อไป*

***ตัววัดที่สำคัญ:*** *จำนวนทารกในครรภ์ที่เป็นโรคธาลัสซีเมียชนิดรุนแรง ซึ่งตรวจพบจากการวินิจฉัยก่อนคลอด*

***ผลการศึกษา:*** *มีสตรีตั้งครรภ์จำนวน 996 คน (ร้อยละ 66.49) ให้ผลการตรวจกรองผิดปกติ ซึ่งในจำนวนนี้สามารถตามสามีมาตรวจเลือดได้ 642 คน (ร้อยละ 64.46) พบคู่เสี่ยงต่อโรคธาลัสซีเมียชนิดรุนแรงจากผลการตรวจทางห้องปฏิบัติการเบื้องต้น 19 คู่ (ร้อยละ1.27 ของสตรีตั้งครรภ์ที่ได้รับการตรวจกรองทั้งหมด) ซึ่งโรคธาลัสซีเมียชนิดรุนแรงที่เสี่ยงมากที่สุด คือ $\beta$-thalassemia/ Hb E diseases จากการศึกษาพบว่ามีสตรีตั้งครรภ์เพียง 10 ราย (ร้อยละ 52.63) ที่ได้รับการวินิจฉัยก่อนคลอดและพบทารกในครรภ์ที่เป็นโรคชนิดรุนแรง 2 ราย (ร้อยละ 20) คือ Hb Bart's hydrops fetalis และ $\beta^{\circ}$-thalassemia/ Hb E disease ซึ่งทั้ง 2 รายนี้ คู่สมรสตัดสินใจยุติการตั้งครรภ์ โครงการนี้สามารถประหยัด ค่าใช้จ่ายที่ต้องเสียในการรักษาผู้ป่วยที่เป็นโรคธาลัสซีเมียชนิดรุนแรงที่ป้องกันได้ 2 รายดังกล่าว 1.14 ล้านบาท*

***สรุป:*** *โครงการป้องกันโรคธาลัสซีเมียชนิดรุนแรงก่อนคลอดที่โรงพยาบาลศรีนครินทร์ สามารถตรวจพบทารกในครรภ์ที่เป็นโรคธาลัสซีเมียชนิดรุนแรงได้อย่างมีประสิทธิภาพ และสามารถลดจำนวนทารกที่เป็นโรคธาลัสซีเมียชนิดรุนแรง ซึ่งเป็นปัญหาสาธารณสุขที่สำคัญของประเทศไทย*