Utilization of healthcare resources and costs of hemolytic disease of fetus and newborn (HDFN) in Israel

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BACKGROUND

Hemolytic disease of the fetus and newborn (HDFN) is a rare and potentially life-threatening condition that occurs when the blood types of the mother and fetus are incompatible, and the mother develops alloantibodies against the antigen on fetal red blood cells (RBC). In severe cases, anemia develops in the fetus which can rapidly progress to fetal hydrops, cardiovascular instability, and death[1,2]. Newborns are at risk of anemia and jaundice which can lead to irreversible damage to the central nervous system if untreated[2,3].

RATIONALE

Important evidence, including the short and long-term implication of the disease and its current management, is still to be generated to facilitate understanding of the full spectrum of the burden of the disease. Such evidence can serve to assess the impact of a potential effective treatment.

OBJECTIVE

There is a knowledge gap of the economic burden of the disease on the healthcare system. This study investigated the extent of healthcare resource utilization (HRU) and costs of HDFN in Israel.

METHODS

A retrospective cohort study on de-identified data from 1998-2021 was performed in Maccabi Healthcare Services (MHS), a 2.6-million-member health plan in. The pregnancy cohort included all pregnancies with a HDFN diagnosis. Offspring from the HDFN pregnancies and children with HDFN diagnosis during their first year of life were included in the newborn cohort, up to the age of 1 year. These children were included in the child cohort from 1 years old until they turned 18, left MHS or died. HDFN diagnosis was defined by ICD-9 or ICD-10 codes excluding ABO alloimmunization. Healthcare resource utilization (HRU) was defined as visits to physicians, surgery, outpatient ER, Hospital ER and hospitalizations. Hospitalization was defined as admissions with at least one overnight stay in hospital. Hospitalization due to delivery/birth were not included, as were not laboratory tests, medical procedures or medication purchases. Costs were assessed using generalized linear models (GLMs) with log link and Gamma distribution. In the child cohort (children aged 1-18 years old), costs analyses were weighted on the number of years through which the children were observed[4].

Mean total cost was calculated as the sum of the mean pregnancy cost, mean annual newborn cost and the mean annual child cost multiplied by 17. Severe HDFN was defined as a pregnancy with at least one of: intrauterine transfusion, fetal hydrops, pre-term labor induction or intrauterine death.

RESULTS & DISCUSSION

Figure 1 – Study cohorts

Pregnancy cohort (N=73)	New-born cohort (N=450)	Child cohort (N=436)
• 73 women diagnosed during pregnancy	• 450 newborns diagnosed until 1 years of age (N=395) and children of women diagnosed during pregnancy (N=55)	• 436 Children with more than 1 year of follow up. • 3 deaths during first year of life, 11 with less than 1 year of follow up

Women diagnosed with HDFN during pregnancy included 73 cases, 20 of which were severe cases. The newborn cohort included 450 newborns - 55 newborns of the aforementioned pregnancies and 395 additional newborns diagnosed with HDFN during their first year. Three newborns died within their first year of life and less than one year of follow up was available for 11 newborns, thus the child cohort consisted of 436 children 1-18 years old (Figure 1).

Table 1 – Healthcare resource utilization

Healthcare Resource Utilization	Median (IQR) of number of visits , N (%)			
	Pregnancy N=73	Severe pregnancy N=20	Newborn N=450	Child N=436
Outpatient ER No. of visits Any visits	2.0 (1.0 -12.0); 3 (4.1%)	0	1.0 (1.0 -2.0); 101 (22.4%)	3.0 (2.0 -5.0); 281 (64.4%)
Hospital ER No. of visits Any visits	1.0 (1.0 -1.0); 8 (11.0%)	1.0 (1.0 -1.0); 2 (10.0%)	1.0 (1.0 -2.0); 59 (13.1%)	2.0 (1.0 -3.0); 130 (29.8%)
Hospitalization* No. of visits Any visits	2.0 (1.0 -2.0); 20 (27.4%)	1.0 (1.0 -2.0); 9 (45.0%)	1.0 (1.0 -2.0); 209 (46.4%)	2.0 (1.0 -3.0); 167 (38.3%)
Ear/nose/throat No. of visits Any visits	NA	NA	1.0 (1.0 -3.0); 96 (21.3%)	3.0 (1.0 -8.0); 273 (62.6%)
Endocrinology No. of visits Any visits	NA	NA	2.5 (2.0 -3.0); 2 (0.4%)	2.0 (1.0 -4.0); 63 (14.4%)
Eyes/ Ophthalmology No. of visits Any visits	NA	NA	1.0 (1.0 -2.0); 109 (24.2%)	3.0 (1.0 -6.0); 316 (72.5%)
Gastroenterology No. of visits Any visits	NA	NA	1.0 (1.0 -1.0); 20 (4.4%)	1.0 (1.0 -3.0); 51 (11.7%)
GP/family med /Paediatrician No. of visits Any visits	2.0 (1.0 -5.0); 41 (56.2%)	1.0 (1.0 -5.0); 8 (40.0%)	16.0 (10.0 -24.0); 445 (98.9%)	69.0 (36.0 -118.0); 424 (97.2%)
Gynecology No. of visits Any visits	3.5 (2.0 -7.5); 68 (93.2%)	3.0 (2.0 -7.0); 15 (75.0%)	NA	1.0 (1.0 -3.0); 48 (11.0%)
Haematology No. of visits Any visits	1.0 (1.0 -1.5); 4 (5.5%)	0	1.0 (1.0 -2.0); 16 (3.6%)	1.5 (1.0 -2.0); 12 (2.8%)
Neurology No. of visits Any visits	NA	NA	1.0 (1.0 -2.0); 18 (4.0%)	, 2.0 (1.0 -5.0); 116 (26.6%)
Surgery No. of visits Any visits	1.5 (1.0 -2.5); 4 (5.5%)	0	1.0 (1.0 -1.0); 43 (9.6%)	2.0 (1.0 -3.0); 110 (25.2%)

Among HDFN pregnancies, 27.4% pregnant women were hospitalized a median of 2 times (IQR 1-2); 91.8% and 56.2% visited a gynecologist and general practitioner, respectively.

Among 20 severe HDFN pregnancies, 45% were hospitalized during pregnancy a median of 1 time (IQR 1-2). During the first year of life, almost half of the newborns were hospitalized and 10% underwent surgery. More than 20% visited an ophthalmologist or an ear nose and throat specialist (ENT).

Many children (1-18 years of age) affected by HDFN were treated by an ENT (62.6%) or an ophthalmologist (72.5%) and a quarter consulted with a neurologist (Table 1).

Table 2 – HRU costs (US $)

Mean pregnancy cost, 95% CI (US$)	Mean annual cost, 95% CI (US$)		Mean total costs 95% CI (US$)
Pregnancy cohort N=73	Newborn N=450	Child N=436	Fetus to 18 years old
1974.9 (1380.1-2825.9)	5988.7 (5341.6-6714.2)	1101.5 (970.4-1250.4)	26689.1 (17946.3 -39691.2)

Mean annual cost of the newborns first year of life was estimated to be 5,988.7 US$ (95% CI 5341.6-6714.2). The average HRU costs through pregnancy, first year of life and up to 18 years of age are estimated to be 26,689.1 US$ (95% CI 17,946.3-39,691.2; Table 2).

CONCLUSION

This study quantified the HRU and costs of an average HDFN case from time of diagnosis during pregnancy until the end of childhood, in Israel. Pregnant women with HDFN are hospitalized at high rates, specifically those with severe HDFN. Moreover, the high frequency of visits to ophthalmologists or ENTs, both in the first year and throughout childhood, may suggest that HDFN-affected children experience long-term audio-visual complications. A previous study comparing costs of newborns diagnosed with CMV to an unexposed control group[5] found the mean annual cost for the unexposed first year of life to be 1037.5 US$, nearly a fifth of the HDFN newborns costs. Further research is needed to corroborate these data and to fully understand the impact of HDFN on healthcare systems.

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