Cutaneous lesions and disorders in healthy term and late-preterm neonates, and their relationships with maternal-neonatal factors

Summary of the Ph.D. Thesis

Rita Ábrahám M.D.

SUPERVISOR: ZSANETT RENÁTA CSOMA M.D., PH.D.

University of Szeged

Albert Szent-Györgyi Medical Centre

Department of Dermatology and Allergology

Szeged

2022

1. Introduction

The neonatal period comprises the first four weeks of life. After birth, the skin has to accommodate to the extrauterine conditions rapidly. Birth, intrapartum traumas, the first encounter with the extrauterine world, microbial colonization, as well as the anatomical and physiological adaptations of the skin, all leave their marks on the integument. Hence, the skin of a mature neonate does not tend to be immaculate; instead, cutaneous lesions are relatively common in the neonatal period. A significant proportion of term, healthy neonates exhibit birthmarks. The exact etiopathogenesis of the symptoms is still unclear, although in part they may be regarded as the consequences of adaptation processes (microbial colonization, thermoregulation, immaturity of vascular innervation). Fortunately, the majority of these cutaneous lesions are physiological, reversible and spontaneously regress. However, the accurate knowledge about neonatal skin lesions is important for several reasons. Regarding birthmarks, it is essential that the neonatologist reassures the inexperienced and anxious parents of the benign nature of these lesions. A prompt and appropriate diagnosis facilitates to avoid unnecessary and prolonged diagnostic and therapeutic procedures. In some cases, transient neonatal dermatosis may present with severe clinical signs, making differential diagnosis difficult. Definitely, cutaneous findings requiring strict observation and follow-up or specific therapy also occur in the neonatal period, and need to be differentiated from benign lesions. Some pigmented lesions, vascular malformations and benign skin tumors are clinically apparent at birth. The appropriate management and treatment of rapidly growing, bleeding hemangiomas are of exceptional importance. In case of severe vascular malformations, further diagnostic investigations are essential to reveal potentially associated abnormalities. Large congenital melanocytic nevi are among the known significant risk factors for melanocytic tumors, therefore their regular dermatologic control is crucial. In addition, up to 300 different types of genodermatoses are known, some of which involve early, congenital cutaneous manifestations. Their early recognition and adequate diagnosis are of great importance.

Although a few epidemiological studies have been conducted to reveal the frequency of neonatal skin conditions, currently only limited and controversial data are available on the etiological factors that influence the development of birthmarks and neonatal skin lesions. To date, no studies are available on the incidence and risk factors of neonatal skin manifestations in a Hungarian population.

2. Aims

1. The aim of our research work was to determine the incidence of cutaneous lesions in a large group of essentially healthy, term or late-preterm Caucasian Hungarian neonates, within the first 72 hours after birth.

2. We also aimed to investigate the relationships between skin findings and six major neonatal and maternal factors (gender, gestational age and birth weight of the neonate; maternal age, number of previous pregnancies, and the mode and circumstances of delivery). These data were collected from the official neonatal medical charts.

3. In a subpopulation of the neonates, further factors underlying the development of neonatal skin findings were examined, using a questionnaire of 37 questions, to get a deeper insight into the neonatal and parental factors that potentially influence the occurrence of neonatal skin disorders. The questionnaire was designed to collect information about a wide range of maternal and several paternal factors, including maternal health, health consciousness and lifestyle habits (acute and chronic diseases of the mother, allergies, skin disorders, smoking, alcohol consumption, dietary supplements, medications), sociodemographic factors (age, marital status, education) and phenotypic characteristics.

3. Methods

After obtaining approval from the Institutional Review Board of the Albert Szent-Györgyi Medical Centre of the University of Szeged, our prospective cohort study was conducted on consecutive neonates born between April 2012 and April 2015 at the Department of Obstetrics and Gynecology at the University of Szeged. During this period 4,658 essentially healthy, term or late-preterm Caucasian Hungarian neonates were examined. Dermatological examinations of the newborns were performed by two dermatologists experienced in pediatric dermatology, and a medical student who had acquired appropriate skills in examining neonates. Only neonates with a stable condition after their first bath were examined for cutaneous lesions within the first 72 hours of life. The entire skin surface, including the scalp, palms, soles, nails and genitalia, was examined carefully. All diagnoses were made on the basis of clinical and morphologic features; no skin biopsy was performed.

Reviewing the official neonatal medical charts of all participating neonates, we collected neonatal history. In addition, in a subgroup of the neonates we supplemented the actual dermatological examination with a questionnaire-based survey (from April 2014 to April 2015) to assess a wider range of maternal and some paternal factors that potentially influence the development of neonatal skin conditions. The standardized questionnaire was completed by a subgroup of 1,629 mothers during the hospitalization period after delivery.

Data were collected and documented using Microsoft® Excel, and statistical analyses were performed using IBM® SPSS Statistics, version 22.0. The associations between skin lesions and neonatal, perinatal and parental features were assessed by the Pearson's chi-squared test and Fischer's exact test. For continuous variables, binary logistic regression, Poisson regression, Kruskal-Wallis analysis and Mann-Whitney U test were performed, setting significance level at $p \leq 0.05$.

4. Results

4.1. Incidence of neonatal skin conditions

A total of 4,658 Caucasian neonates (48.54% females and 51.46% males) were examined. Gestational age at birth ranged between 34 and 42 weeks (mean gestational age: 38.9±1.2 weeks). Mean birth weight was 3,373.7±469.1 gramm; mean birth length was 49.7±2.0 cm. Mean birth weight and birth length of male neonates were significantly higher than those of the females (p=0.001). The rate of vaginal delivery was 56.35%, operative vaginal delivery with the use of vacuum extractor or forceps was required in 86 cases. 43.65% of the newborns were born by caesarean section. Average maternal age was 30.9±5.3 years. Older maternal age significantly correlated with a higher birth weight of the newborns (p=0.001). The average number of pregnancies per women equalled to 2.2±1.4, with an average number of children born to a mother equalling to 1.8±0.97. The average birth weight of infants born to primiparas was significantly lower than that of those born to multiparas (p=0.001). Meconium-stained amniotic fluid was documented in 169 cases. We found a significant correlation between primiparity and the occurrence of meconium-stained amniotic fluid (p=0.001).

74.35% of the neonates exhibited at least one skin manifestation. These cutaneous findings were assigned to five categories (**Table 1**). The correlations revealed between skin findings and the six major neonatal and maternal factors examined are summarized in **Table 2**.

CUTANEOUS LESIONS	TOTAL N (%)	FEMALE N (%)	MALE N (%)	P-VALUE
TRANSIENT, BENIGN SKIN LESIONS				
*Sebaceous gland hyperplasia **	1,365 (29.30)	613 (27.11)	752 (31.37)	**0.001 ***
Erythema toxicum neonatorum	1,060 (22.76)	487 (21.54)	573 (23.90)	0.054
Dry, desquamating skin	353 (7.58)	160 (7.08)	193 (8.05)	0.209
Milia	126 (2.71)	57 (2.52)	69 (2.88)	0.452
Miliaria crystallina	53 (1.14)	24 (1.06)	29 (1.21)	0.633
Neonatal cephalic pustulosis	22 (0.47)	10 (0.44)	12 (0.50)	0.772
Acrocyanosis	8 (0.17)	3 (0.13)	5 (0.21)	0.727
Transient neonatal pustular melanosis	4 (0.09)	0 (0.00)	4 (0.17)	0.125
VASCULAR LESIONS *				
*Nevus simplex **	1,796 (38.56)	977 (43.21)	819 (34.17)	**0.001 ***
*Hemangioma precursor lesion **	109 (2.34)	64 (2.83)	45 (1.88)	**0.031 ***
Hemangioma	30 (0.64)	15 (0.66)	15 (0.63)	0.872
Cutis marmorata	30 (0.64)	17 (0.75)	13 (0.54)	0.372
Port-wine stain	30 (0.64)	17 (0.75)	13 (0.54)	0.372
SKIN INJURIES OF TRAUMATIC, IATROGENIC, CONGENITAL OR ACQUIRED ORIGIN *				
Hematoma, petechiae	266 (5.71)	116 (5.13)	150 (6.26)	0.097
Laceration	74 (1.59)	41 (1.81)	33 (1.38)	0.234
Caput succedaneum	65 (1.4)	25 (1.11)	40 (1.67)	0.102
*Erosion **	20 (0.43)	4 (0.18)	16 (0.67)	**0.010 ***
Diaper dermatitis	14 (0.30)	9 (0.40)	5 (0.21)	0.238
Aplasia cutis congenita	5 (0.11)	2 (0.09)	3 (0.13)	1.000
Intrauterine scar	3 (0.06)	1 (0.04)	2 (0.08)	1.000
Vesiculae, bullae	3 (0.06)	0 (0.00)	3 (0.13)	0.250
Transient neonatal bullous dermolysis	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Epidermolysis bullosa	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Enterovirus infection induced skin lesions	1 (0.02)	0 (0.00)	1 (0.04)	1.000
PIGMENTED LESIONS				
Mongolian spot	144 (3.09)	73 (3.23)	71 (2.96)	0.599
Congenital melanocytic nevus	73 (1.57)	41 (1.81)	32 (1.34)	0.189
Café-au-lait macule	20 (0.43)	6 (0.27)	14 (0.58)	0.096
Blue nevus	6 (0.13)	3 (0.13)	3 (0.13)	1.000
Lentigo	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Linear nevoid hypermelanosis	1 (0.02)	1 (0.04)	0 (0.00)	0.485
DEVELOPMENTAL ABNORMALITIES, BENIGN SKIN TUMORS AND CYSTS				
Benign skin tumors and cysts	42 (0.90)	18 (0.80)	24 (1.00)	0.459
Accessory tragus	14 (0.30)	7 (0.31)	7 (0.29)	0.913
Supernumerary nipple	10 (0.21)	4 (0.18)	6 (0.25)	0.755
Tooth	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Nevus sebaceous	1 (0.02)	1 (0.04)	0 (0.00)	0.485
Congenital lymphoedema	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Minor anomalies	1 (0.02)	1 (0.04)	0 (0.00)	0.485

Table 1. *The frequency of cutaneous lesions detected in a population of 4,658 neonates within the first 72 hours of extrauterine life, and the distribution of skin manifestations according to gender (Pearson's chi-squared test, Fischer's exact test; *: p≤0.05)*

CUTANEOUS LESIONS	RELATED PARAMETER	P -VALUE
TRANSIENT, BENIGN SKIN LESIONS	**male gender**	**0.001**
	higher gestational age	**0.021**
Sebaceous gland hyperplasia	male gender	0.001
	lower gestational age	0.001
	older maternal age	0.005
Erythema toxicum neonatorum	higher gestational age	0.001
	higher birth weight	0.001
Dry, desquamating skin	higher gestational age	0.001
	higher birth weight	0.024
	spring birth	0.001
	meconium-stained amniotic fluid	0.001
Milia	higher gestational age	0.001
	higher birth weight	0.001
VASCULAR LESIONS	**female gender**	**0.001**
	higher gestational age	**0.010**
Nevus simplex	female gender	0.001
	higher gestational age	0.020
Hemangioma precursor lesions	females	0.031
Cutis marmorata	lower gestational age	0.001
	lower birth weight	0.001
	caesarean section	0.003
SKIN INJURIES OF TRAUMATIC, IATROGENIC, CONGENITAL OR ACQUIRED ORIGIN	**male gender**	**0.050**
	higher birth weight	**0.001**
	primiparity	**0.001**
	vaginal delivery	**0.001**
	operative vaginal delivery	**0.001**
Hematoma, petechiae	higher birth weight	0.001
	primiparity	0.001
	vaginal delivery	0.001
	operative vaginal delivery	0.001
Caput succedaneum	primiparity	0.001
	vaginal delivery	0.001
	operative vaginal delivery	0.009
Erosion	male gender	0.010
Diaper dermatitis	lower gestational age	0.006
PIGMENTED LESIONS	**younger maternal age**	**0.001**
Mongolian spot	lower maternal age	0.001

Table 2. *Significant correlations were revealed between the incidence of numerous cutaneous findings and neonatal, maternal and perinatal factors (Pearson's chi-squared test, Fischer's exact test, binary logistic regression, significance level: $p \leq 0.05$; N=4,658)*

4.2. Results of our detailed questionnaire-based substudy

4.2.1. Patient characteristics

A total of 1,629 Caucasian neonates were included in this substudy (849 males and 780 females). Gestational age ranged between 34 and 41 weeks. Birth weight ranged from 2,060 to 4,930 gramm. The rate of vaginal deliveries was 57.6%, while 42.4% of the infants were born by caesarean delivery. Operative vaginal delivery with the use of vacuum extractor or forceps was performed in 32 cases. Mean 1-minute Apgar score was 9.1±1.1. The mean length of hospitalization was 3.8±1.5 days. The average gestational age at birth was similar in females and males, whereas the birth weight of male infants was significantly higher compared to females (p=0.001). A significantly higher proportion of males (45.6%) were born by caesarean section than females (39.0%) (p=0.007). The frequency of caesarean delivery decreased with increasing gestational age (p=0.001). The Apgar score of infants born before week 37 of gestation was significantly lower (8.68±1.44) than that of mature neonates (9.10±1.12) (p=0.004). Meconium-stained amniotic fluid was significantly more frequently associated with vaginal than caesarean delivery (p=0.027). These findings correlate with those demonstrated in the full population (N=4,658 neonates).

4.2.2. Sociodemographic factors/characteristics

In our detailed questionnaire-based substudy, maternal age at delivery ranged from 13 to 48 years, whereas paternal age was between 18–59 years. Maternal age significantly correlated with a higher birth weight of the newborns (p=0.001); the rate of high birth weight infants was significantly higher for mothers over 35 years of age (p=0.001). The frequencies of caesarean section (p=0.001), maternal hypertension (p=0.035) and maternal diabetes/insulin resistance (p=0.013) (both diagnosed either before or during pregnancy) increased with increasing maternal age. The average number of pregnancies per woman equalled 2.2±1.4, with an average number of children born to a mother equalled to 1.8±0.9. Mean birth weight of the infants for primiparas was significantly lower than that for multiparas (p=0.001). Significant correlation was detected between primiparity and the occurrence of meconium-stained amniotic fluid (p=0.019).

Regarding the marital status of mothers, 58.5% was married, 38.7% was never married, and 2.8% was divorced or widowed. Regarding education, 47.8% of the mothers and 35.1% of

the fathers graduated from university, and 17.6% of the mothers and 32.6% of the fathers completed primary education only. The average birth weight of the infants was highest in the group of married mothers (3,398.6 gramm *vs*. 3,315.4 gramm for maiden mothers and 3,393.3 gramm for divorced or widowed mothers), however, regarding gestational age at birth no differences were found among the three groups. Neonatal birth weight significantly increased with the parents' level of education (p=0.001).

4.2.3. Maternal health, health consciousness and lifestyle habits

Pre-pregnancy body mass index (BMI) was low (<18.5) for 83 mothers (5.2%), normal (18.5–25.0) for 969 (60.2%) and high (>25.0) for 557 mothers (34.6%). BMI significantly increased with age (p=0.001). Maternal BMI significantly correlated with neonatal birth weight (p=0.001) and caesarean delivery (p=0.001). Apgar scores for the newborns of mothers with normal pre-pregnancy BMI were significantly higher than those for the infants born to mothers with low or high BMI (p=0.005).

Any acute or chronic diseases diagnosed before or during pregnancy were reported by 68.7% of the mothers, the most frequent being upper respiratory tract (n=683) and other infections (n=436), followed by maternal hypertension (n=136), diabetes mellitus/insulin resistance (n=186) and hypothyroidism (n=79). The frequency of maternal hypertension (p=0.035) and diabetes/insulin resistance (p=0.013) increased with increasing maternal age. In the subgroup with hypertension, the frequency of caesarean delivery was significantly higher compared to vaginal delivery (58.5% *vs.* 41.5%; p=0.001). The frequency of both maternal (33.1%) and paternal (23.4%) allergies (hay fever, drug hypersensitivity, atopic dermatitis, food allergy, asthma and conjunctivitis) were reported to be high.

Four hundred and thirty-six mothers reported taking medication regularly, while 45.9% took some medication occasionally during pregnancy. For infants with mothers taking medication regularly during pregnancy, gestational age at birth was significantly lower (p=0.001) than for those born to mothers taking no medications during pregnancy. Also, significantly more infants were born by caesarean delivery to mothers taking medication regularly during pregnancy, as compared those whose mothers took no medication (p=0.005). The frequency of preterm delivery was higher for mothers taking non-steroidal anti-

inflammatory drugs (NSAIDs) during pregnancy (p=0.012) compared to those not taking NSAIDs.

Dietary supplements were taken by 32.8% of the mothers before and 92.1% during pregnancy. The frequency of preterm delivery was significantly higher among those not taking multivitamin supplements (5.7% *vs.* 3.5%, p=0.029). The frequency of caesarean delivery was significantly lower for mothers using homeopathic remedies advised for preparing for labor (p=0.018). Our questionnaire-based substudy included 1,028 mothers who had used oral contraceptives (OCs) before pregnancy, and 11 of those continued to use OCs during the first few weeks of pregnancy. Regarding smoking, 24.1% (N=389) of the mothers smoked in the six months before pregnancy, and 55 (3.41%) also smoked regularly during pregnancy. A further 16.6% was exposed to tobacco smoke during pregnancy at workplace and 18.5% at home. We found a significant correlation between lower birth weight and smoking before (p=0.009) or during pregnancy (p=0.001). In total, 60.7% of the mothers consumed alcohol in the six months before pregnancy, and 15.9% consumed alcohol occasionally during pregnancy.

4.2.4. Phenotypic characteristics

Our questionnaire-based substudy assessed pigmentary traits, specifically maternal and paternal hair, eye and skin colors, as well as skin phototype. Skin phototype was assessed on the Fitzpatrick scale, which is based on a person's reaction to 30 minutes of midday sunlight for the first time in the summer.

5. Discussion

5.1. Transient, benign skin lesions

5.1.1. Sebaceous gland hyperplasia (SGH)

SGH was observed in 29.30% of the neonates. In our cohort, there was a significantly higher incidence of SGH in males. In agreement with Nanda *et al.*, we found that SGH was significantly more common in neonates of younger gestational age. Moreover, a significantly higher incidence of SGH was revealed for infants whose mothers suffered from acute or chronic diseases, particularly hypertension or diabetes/insulin resistance. These findings may be explained by the elevated levels of androgens in hypertension and insulin resistance, as androgens are known to play a role in the development of SGH.

5.1.2. Erythema toxicum neonatorum (ETN)

Based on previous reports, the frequency of ETN varies widely between 1.3% and 40.8%; in our study population the incidence was 22.76%. Literature reports on the predisposing factors of ETN are conflicting. In accordance with several previous studies, we found a significant correlation between ETN and a higher gestational age or birth weight. Moreover, we found significant correlations between ETN and multivitamin use, as well as vitamins C, D, E and iodine supplementation during gestation. As both the infant's maturity and vitamin supplementation are likely to contribute to the appropriate function of the immune system, our findings agree with the most generally accepted view that ETN is a consequence of a cutaneous immunological response to microbial colonization. In addition, we found a significant correlation between the incidence of ETN and parental atopic dermatitis, which also supports the role of the immune system in the development of ETN, further confirmed by the finding that eosinophils were identified in the pustules.

5.1.3. Jaundice

Jaundice was observed for 17.37% of the newborns, which is in the range reported in other studies (0.3–25.6%). Significant correlations were found between jaundice and male gender, younger gestational age, vaginal delivery, primiparity and a higher maternal pre-pregnancy BMI. Unlike Monteaguado *et al.*, we did not reveal associations between neonatal jaundice and maternal use of iodine, folic acid and iron supplementation during pregnancy. However, our findings indicate a significantly higher incidence of jaundice in newborns whose mothers were prescribed magnesium supplementation during pregnancy. Previously, Sarici *et al*. found a positive correlation between the increase of serum ionized magnesium levels and the severity of hyperbilirubinemia. The length of hospitalization was significantly longer for infants with jaundice than those without it.

5.1.4. Dry, desquamating skin

Dry skin with desquamation was detected in 7.58% of the neonates. We have revealed significant correlations between the incidence of this transient skin condition and spring birth, vaginal delivery, meconium-stained amniotic fluid. Moreover, in accordance with several other studies, the frequency of dry, desquamating neonatal skin increased with increasing gestational

age. A potential explanation for this finding is that newborns delivered after 40 weeks of gestation experience a longer exposure to the amniotic fluid, which might disrupt the lipid lamellae in stratum corneum. Consequently, the formation of stratum corneum is accelerated, resulting in hyperproliferation and inadequate cell loss manifested as desquamation. In addition, a significantly higher incidence of dry, desquamating skin was evident in infants whose mothers smoked in the six months before or during pregnancy.

5.1.5. Other benign, transient lesions

Hypertrichosis was seen in 6.08% of the infants, and was associated with a higher maternal pre-pregnancy BMI, as well as with darker maternal and paternal eye, hair and skin colors. Milia were detected in 126 (2.71%) newborns. Our findings confirm previous reports that milia are more common in mature infants, whereas the frequency of miliaria decreased with increasing infant maturity. Neonatal cephalic pustulosis is rare in newborns; its incidence was 0.47% in our study. According to the literature, the incidence of transient neonatal pustular melanosis ranges from 0.3% to 3.4%. In our study its incidence was 0.09%.

5.2. Vascular lesions

5.2.1. Nevus simplex (NS)

Vascular lesions were observed frequently in our study, occurring in 40.68% of the newborns. Of these vascular cutaneous conditions, NS was the most common, colloquially often referred to as „salmon patch", „stork bite" or „angel kiss". The macules, varying in color from pale-pink to bright-red, are most frequently localized to the nape, to the upper eyelids symmetrically, or to the glabella along the embryogenic fusion lines. Also, it may appear along the midline, and rarely some atypical locations are also probable. NS is not a real vascular malformation, but is presumed to result from the transient immaturity of vascular innervation and the persistence of local fetal circulation. Most of these macules disappear spontaneously between the ages of 1 and 3 years, but residual lesions may remain. Long-lasting NS lesions tend to be localized to the nuchal area, so that cosmetic concerns rarely arise. Prominent or persistent NS is rarely associated with various developmental abnormalities or syndromes.

In previous literature reports the frequency of NS varies widely, between 0.4% and 83.0%; in our study population the incidence of NS was 38.56%. We found a significantly higher incidence in females and in neonates with a higher gestational age.

5.2.2. Nevus flammeus asymmetricus (port-wine stain (PWS))

Nevus flammeus asymmetricus is a true capillary vascular malformation. The lesions persist throughout life, and tend to become darker, infiltrated and nodular over time. Its prevalence in neonates is reported to range between 0.04% and 3.3%. In our study the rate was 0.64%. A significantly higher frequency of PWS was evident in infants whose mothers continued to use OC during the gestation period. Increased awareness of certain syndromes associated with capillary malformations is of great importance. When PWS appears in the region of the ophthalmic branch of the trigeminal nerve, the possibility of Sturge–Weber syndrome arises. In case of a clinical suspicion, ophthalmological and neurological examinations and a close follow-up of the neonate are crucial. PWS may also be a finding in Klippel–Trenaunay syndrome, which involves a combination of lymphatic, venous and capillary malformations, varicose veins and the overgrowth of soft tissue or bone, affecting mainly the lower extremities.

5.2.3. Hemangiomas

Hemangiomas typically appear shortly after birth (infantile hemangiomas), although in some cases (1.1–2.6%) these lesions are already present at birth (congenital hemangiomas). At birth, the sites of subsequent hemangiomas are often indicated by a telangiectatic patch surrounded by a pale halo. Hemangiomas tend to involute, and disappear after infancy, without any sequelae. In 10–15% of all cases, serious complications, including ulceration, bleeding, infection, deformation of the bones or soft tissues, congestive heart failure and permanent aesthetic deformations may emerge. Hemangiomas around the eyes or ears may lead to sensory organ dysfunction. In case the hemangiomas are localized around the nose or the subglottic region, airway obstruction is a frequent, life-threatening complication. Hemangiomas in the lumbar and sacral region may be associated with spine and spinal cord malformations, while multiplex hemangiomas may be part of a syndrome with systemic manifestations.

Our study has revealed hemangiomas in 0.64% of the neonates, while a further 2.34% exhibited teleangiectic macules possibly corresponding to an incipient hemangioma.

Significant associations were found between the appearance of these lesions and paternal phenotypic characteristics, including lighter eye and hair colors.

5.2.4. Cutis marmorata

In our study, physiological cutis marmorata was more common in neonates born by caesarean section than in those born vaginally. Additionally, correlations were revealed between the presence of cutis marmorata and lower gestational age and birth weight. This association may reflect the greater vulnerability of these neonates, who are therefore more likely to present with adaptation disorders and vasomotor instability. In our cohort, cutis marmorata was also significantly associated with maternal hypertension and smoking during gestation. Regarding differential diagnosis, cutis marmorata telangiectatica congenita, a rare, sporadic vascular malformation, should be considered.

5.3. Pigmented lesions

5.3.1. Mongolian spots (MSs)

In our study, pigmented lesions were detected in 232 neonates (4.98%), of which MSs were the most frequent. MSs are well-defined, bluish grey macules of various size, generally localized to the lumbosacral or sacrococcygeal area, but the lesions may also occur on the shoulders, back and lower extremities. The macules tend to fade and disappear with time, but may also persist in rare cases. If the lesions are persistent, multiple or extended, they may be associated with developmental abnormalities (cheiloschisis), metabolic disorders (GM1 gangliosidosis or mucopolysaccharidosis type II), or phacomatosis pigmentovascularis or phacomatosis pigmentopigmentalis. Regarding differential diagnosis, bruises resulting from physical abuse should be assessed. The prevalence of MSs varies widely among different racial and ethnic groups: they are much more common in black, native American, Asian and Hispanic populations (60–90%). In our study, the incidence of MSs was much lower: 3.09%, with a higher incidence in infants whose parents were more pigmented. Moreover, the frequency of MSs was found to decrease with increasing maternal age.

5.3.2. Other pigmented lesions

In infants with a darker pigmentation, genital hyperpigmentation (GH) is a common finding. In agreement with other reports, GH was more common in males. In our study, a significant correlation was found between GH and darker parental eye, hair and skin colors. In addition, we found a positive correlation with higher maternal weight gain during pregnancy. These observations suggest that hormonal factors might have a role in the pathogenesis of GH.

According to the literature, the incidence of congenital melanocytic nevus (CMN) is around 0.2–2.7%; we detected CMN in 1.57% of the neonates. In our study, most CMNs' diameter did not exceed 10 mm, the largest being 90×65 mm. Regarding its potential for a malignant transformation, dermato-oncologic observation for all CMN lesions is crucial.

Café-au-lait macules (CALMs) are highly common, affecting 10–30% of the population. In our study population the incidence was 0.43%, and only soliter lesions were detected. Multiplex CALMs are rarely seen, and may be related to genetic diseases, of which neurofibromatosis is probably the best known and most common diagnosis. However, several other, rare disorders should also be considered for differential diagnosis.

5.4. Other cutaneous findings

5.4.1. Skin injuries of traumatic, iatrogenic, congenital or acquired

In our study population, 9.17% of the neonates were affected by skin injuries of traumatic, iatrogenic, congenital or acquired origin, of which hematoma and petechiae were the most common (266 cases), followed by laceration (74 cases) and caput succedaneum (65 cases). The occurrence of these traumatic lesions significantly correlated with primiparity, vaginal delivery and higher birth weight. It can be speculated that a larger neonate, a higher rigidity of pelvic structures and a tighter birth canal of primiparous women may predispose to these types of skin injuries, as these characteristics make fetal passage through the birth canal more difficult. Traumatic lesions were significantly more frequent in male than in female neonates, which may be explained by the significantly higher birth weight and birth length of male infants.

Our survey revealed significant associations between primiparity, vaginal delivery and caput succedaneum. This confirms a causative role of birth trauma in the etiology of caput succedaneum. Moreover, a significantly higher proportion of neonates born vaginally and/or with a higher birth weight exhibited hematoma or petechiae. As expected, following operative

vaginal delivery with the use of a vacuum extractor or forceps, the incidence of traumatic skin lesions, including hematoma or petechiae and caput succedaneum were also significantly higher.

Disorders with skin defects cannot only result from traumas, but may also be related to congenital conditions. Probably the best known of these is aplasia cutis congenita, which was detected in 5 cases in our study.

Diaper dermatitis primarily occurs in young infants aged a few months old. In our study its incidence was 0.30%. Sadana *et al*. reported a significantly higher incidence of diaper dermatitis in mature infants of lower birth weight, while we have revealed a significant correlation with lower gestational age.

Other skin injuries of traumatic, iatrogenic, congenital or acquired origin were observed in a few newborns only. Clinical diagnoses included intrauterine scar (3 cases), transient neonatal bullous dermolysis (1 case) and epidermolysis bullosa simplex (1 case). A male infant presented with numerous small erosions and vesicules surrounded by an erythematous halo, corresponding to a diagnosis of congenital enterovirus infection.

5.4.2. Developmental abnormalities, benign skin tumours

In our study 1.5% of the neonates were diagnosed with developmental abnormalities, including accessory tragus (0.30%), supernumerary nipple (0.21%) or tooth (0.02%), congenital lymphoedema (0.02%) and some minor anomalies (0.02%). Also, some benign skin tumors (fibromas, cysts) were detected. Significant correlation was found between vitamin A supplementation during pregnancy and the incidence of developmental abnormalities, as well as benign skin tumors and cysts, which is consistent with the teratogenic effect of vitamin A and its synthetic derivatives. This association was further strengthened when PWSs were included in the disease group of developmental abnormalities. Nevus sebaceous was diagnosed in one neonate.

6. Summary

Epidemiological studies report on the incidence and risk factors for a great variety of neonatal skin conditions; however, to the best of our knowledge, our study is the most comprehensive research work into skin conditions specific to this age group to date.

Our study was performed at one of the largest university clinics in Hungary, and involved over 4,600 neonates in a 3-year-period, therefore it can be considered as a representative sample. Our findings are readily comparable with published research works in this field, and are in agreement with those in several aspects. Regarding the incidence of some common skin conditions, such as NS, ETN, SGH, and MSs, significant differences are evident among different countries and races. Such differences may partially be explained by geographical and climatic factors affecting the development of various skin manifestations. The frequency of some cutaneous lesions (e.g. MSs) differs significantly as a function of skin type and skin pigmentation in various ethnic groups. Some neonatal skin lesions (e.g. ETN) are characterized by relatively rapid changes, thus the timing of dermatologic examinations determines the actual findings. Diagnostic criteria may also differ among neonatal centers, possibly leading to different findings.

The results of our study confirm that the vast majority of neonatal dermatologic lesions are benign and require no specific therapy. However, the great variety of cutaneous findings underlines the importance of a thorough and up-to-date knowledge of skin manifestations for dermatologist and pediatricians, as well as the significance of patient education to improve health literacy of the parents. Our study supports that gender, gestational age and birth weight of the neonate play a significant role in the development of neonatal cutaneous lesions. In addition, our findings suggest that sociodemographic factors, parental phenotypic characteristics, maternal hormones, and the presence of acute and chronic diseases of the mother may also contribute to the development of specific cutaneous lesions. Our study seems to provide an accurate and comprehensive picture of the dermatological conditions occurring in otherwise healthy, mature (term or late-preterm) neonates. A detailed study of numerous factors playing a role in the development of neonatal skin lesions contributes to the clarification of the exact etiopathological background of these skin conditions.

ACKNOWLEDGEMENTS

First of all, I would like to thank my supervisor, **Dr. Zsanett Renáta Csoma**, for providing me with the opportunity to accomplish my scientific work. I would like to express my deep gratitude for her invaluable assistance, patient guidance, never-ending enthusiasm, and useful critiques of my work.

I would like to say special thanks to **Prof. Lajos Kemény**, who provided me with the opportunity of working at the Department of Dermatology and Allergology.

I am particularly grateful for the assistance and support from **Prof. Hajnalka Orvos** from the Department of Obstetrics and Gynecology, who allowed me to perform my work at the Neonatal Care Unit.

I also wish to acknowledge the help provided by **Dr. Judit Bakki** and **Dr. Zita Gyurkovits**.

I would also like to extend my thanks to **Dr. Éva Viharosné Dósa-Rácz** and **Andrea Gyimesi** for their technical support.

Last but not least, I am thankful to **all the nurses working at the Neonatal Care Unit**, for helping with the examinations of the neonates.

Also, I thank **Dr. Dóra Bokor** for proofreading my thesis.

Finally, I wish to thank **my family** for their support and encouragement throughout my studies and life.

Publications directly related to the subject of the thesis

I. Csoma Z, Meszes A, **Ábrahám R**, Bakki J, Gyurkovits Z, Kemény L, Orvos H. Születési jegyek, újszülöttkori bőrelváltozások. Az angyalcsóktól az epidermolysis bullosáig. *Orv Hetil* 2014;155:500–508.

II. Csoma Z, **Ábrahám R.** Születési jegyek, gyakori újszülöttkori bőrelváltozások. *Gyermekgyógy Továbbk Szle* 2016;21:151–155.

III. **Ábrahám R**, Meszes A, Bakki J, Gyurkovics Z, Terhes G, Orvos H, Csoma Z. Kongenitális enterovírus-infekció. *Gyermekgyógyászat* 2016;67:13–15.

IV. Csoma Z., Meszes A, **Ábrahám R**, Kemény L, Tálosi Gy, Doró P. Iatrogenic skin disorders and related factors in newborn infants. *Pediatr Dermatol* 2016;33:543–548.

V. **Ábrahám R**, Varga E, Tóth-Molnár E, Kemény L, Csoma Z. Multiplex juvenilis xanthogranuloma. *Bőrgyógyász Venerol Szle* 2017;93:291–294.

VI. **Ábrahám R**, Meszes A, Kemény L, Gyurkovits Z, Bakki J, Orvos H, Csoma Z. Cutaneous lesions in healthy neonates and their relationships with maternal-neonatal factors: a cross-sectional study. *World J Pediatr* 2017;13:571–576.

VII. Csoma Z., Dalmády S., **Ábrahám R**., Rózsa T., Rácz K., Kemény L.: Infantilis haemangioma: klinikai és demográfiai jellemzők, kezelési-gondozási tapasztalatok. *Orv Hetil* 2017;158:1535–1544

VIII. **Ábrahám R**, Kemény L, Csoma Z. Újszülöttkori bőrelváltozások: veszélyes vagy ártalmatlan? Kövessük, gondozzuk, kezeljük? *Bőrgyógyász Venerol Szle* 2018;94:7–13.

IX. **Ábrahám R**, Gyurkovits, Z, Bakki J, Orvos H, Kemény, L, Csoma Z. A születési jegyek és az újszülöttkori bőrgyógyászati elváltozások kialakulásában szerepet játszó tényezők vizsgálata. *Orv Hetil* 2022;163:513–522.

Publications not closely related to the subject of the thesis

I. **Ábrahám R**, Csoma Z. Az acne vulgaris és kezelése. *Gyermekorvos Továbbképzés* 2019;18:55–57.